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UMANG KHETARPAL, MD
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IN SEARCH OF PATHOLOGIC CORRELATES FOR HEARING LOSS AND VERTIGO IN PAGET'S DISEASE

A CLINICAL AND HISTOPATHOLOGIC STUDY OF 26 TEMPORAL BONES

UMANG KHETARPAL, MD

HAROLD F. SCHUKNECHT, MD

BOSTON, MASSACHUSETTS

Mixed sensorineural and conductive hearing loss is a common clinical manifestation of Paget's disease of the temporal bone, and while there are numerous clinical and pathologic reports on the condition, none have identified a consistent pathologic explanation for the hearing loss. We performed histologic studies on 26 temporal bones exhibiting Paget's disease from 16 persons, of whom 7 had audiometric testing performed. Contrary to common opinion, the conductive hearing loss is not caused by ossicular fixation; in fact, no cause could be found in the seven ears with documented conductive hearing losses. While the sensorineural hearing losses were greater than normal for age, we could not identify cochlear disorders that could be attributed to Paget's disease. It is concluded that the hearing losses in Paget's disease are caused by changes in bone density, mass, and form that serve to dampen the finely tuned motion mechanics of the middle and inner ears.

KEY WORDS — deafness, hearing loss, osteitis deformans, Paget's disease, temporal bone pathology.

It is estimated that about 50% of persons with Paget's disease of the temporal bones have hearing losses greater than normal for age.¹ The hearing impairment may be sensorineural,¹⁻⁶ mixed,^{5,7-9} or, rarely, only conductive.¹⁰ Most often the pattern is a mixed loss with the sensorineural loss simulating presbycusis. The literature contains numerous clinical^{4-7,11-14} and histologic^{1,5,7,10-12,15-19} reports on Paget's disease, yet none have clearly identified a consistent pathologic basis for these hearing losses. The histologic and clinical findings that have been reported in the literature are summarized in Tables 1^{1,3,4,6,10-12,14,16,19-29} and 2.^{1,5,7,11,12,15-23,27-29} In many instances the relationship of pathologic findings to hearing loss is speculative and poorly documented, and little consideration has been given to the possible coexistence of other disorders, particularly the effects of aging on the inner ear.

In an attempt to resolve this dilemma, we have performed histologic studies on 26 temporal bones of 16 persons who had Paget's disease of the temporal bones. Twelve temporal bones from 7 of these subjects had audiometric data that permitted a correlation of hearing losses and temporal bone pathologic findings.

METHOD

The temporal bones were prepared for light microscopic study in the usual manner by fixation with Heidenhain-Susa solution, decalcification in trichloroacetic acid, dehydration in alcohol, and embedding in celloidin. Serial sections were cut at a thickness of 20 μ m, and every 10th section was stained with hematoxylin and eosin and mounted

on a glass slide. The cochleas of the 12 temporal bones for which audiograms were available were graphically reconstructed.^{30,31} A determination was made of the presence or absence of inner and outer hair cells at approximately 100 locations in each ear where the organs of Corti were cross-sectioned. Atrophy of the striae vasculares was based on visual judgments of the volume of stria remaining in each millimeter.

The cochlear neurons were counted in approximately 33 locations at which the spiral ganglia had been sectioned, and calculations were made to determine the neuronal populations in four segments of the cochleas as well as the total number.³² Judgments were also made of the quantity of dendritic fibers present.³³ For the comparison of neuronal counts in each case with the average normal count for age, the normative data of Otte et al³² were used. A best-fit line was drawn through the points (originally plotted by Otte et al) representing total neuronal counts at each decade. The line has a slope of 2,100 cells per decade and represents the average neuronal counts at each decade. For the decade 91 to 100 years, normative data are not available; thus, the best-fit line was extended and the extrapolated count for this decade was obtained. By use of mathematic calculations, the old data for segmented counts were modified to fit the "new" total neuronal counts. Cytocochleograms of comparative neuronal counts in the 12 ears reconstructed were based on this new data base.

The audiograms and cytocochleograms are displayed on parallel coordinates. The frequencies of the audiogram have been distributed on the abscissa

From the Department of Otolaryngology, Harvard Medical School, and the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. Supported by grant R01 DC00079 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

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TABLE 1. REPORTED PATHOLOGIC FINDINGS IN CONDUCTIVE HEARING LOSS CAUSED BY PAGET'S DISEASE

<i>Pathologic Findings</i>	<i>No. of Ears</i>	<i>Authors</i>	<i>Year</i>	<i>Basis</i>
External auditory canal narrowing	1	Fowler ³	1937	Clinical
	1	Sparrow and Duvall ¹⁴	1967	Clinical
	1	Nager ¹	1975	Histologic
Tympanic membrane fibrosis	1	Tamari ¹⁰	1942	Histologic
	1	Nager ¹	1975	Histologic
Tympanic membrane laxity	1	Tamari ¹⁰	1942	Histologic
	1	Griffey ¹⁶	1960	Clinical
	1	Nager ¹	1975	Histologic
	1	Applebaum and Clemis ²⁰	1977	Histologic
Tympanic annulus calcification	1	Nager and Mayer ¹²	1932	Histologic
	1	Nager ¹	1975	Histologic
Eustachian tube obstruction	1	Sparrow and Duvall ¹⁴	1967	Speculation
	1	Nager ¹	1975	Speculation
Tympanic cavity fibrosis and ossification; otitis media	5	Tamari ¹⁰	1942	Histologic
	2	Sparrow and Duvall ¹⁴	1967	Clinical
	1	Lindsay and Lehman ²¹	1969	Histologic
	1	Proops et al ¹⁹	1985	Clinical
	1	Friedmann ²²	1974	Histologic
Malleus and/or incus fixation	2	Gussen ²³	1970	Clinical
	1	Nager ¹	1975	Histologic
	1	Proops et al ¹⁹	1985	Histologic
Stapes fixation or resorption; some with otosclerosis	1	Mayer ¹¹	1917	Histologic
	2	Mayer ²⁴	1928	Histologic
	1	Goodhill ²⁵	1960	Clinical
	2	Waltner ²⁶	1965	1 Clinical, 1 histologic
	1	Goodhill ²⁷	1967	Histologic
	1	Friedmann ²²	1974	Histologic
	1	Nager ¹	1975	Histologic
	2	Lindsay and Suga ²⁸	1976	Histologic
	2	Clemis et al ⁴	1967	Clinical
	17	Harner et al ⁶	1978	Radiographic
Round window niche obliteration	2	Kelemen ²⁹	1977	Histologic
	1	Proops et al ¹⁹	1985	Histologic
	1	Nager and Mayer ¹²	1932	Histologic
	1	Nager ¹	1975	Histologic

in accordance with their loci along the cochlear duct as determined by a newly derived "data-based" anatomic frequency scale (H. F. Schuknecht, unpublished data). Cochleas that were longer or shorter than 32 mm were contracted or expanded to fit the standard 32-mm scale representing cochlear length.

HISTOPATHOLOGY OF PAGET'S DISEASE

Normal lamellar bone has a parallel arrangement of collagen fibers, relatively few osteocytes per unit area of matrix, and a uniformity in size and shape of the osteocytes, which are generally small cells with dark nuclei.³⁴ There is general agreement that pagetic bone changes can be divided into three phases³⁴⁻³⁶; however, in the temporal bone a fourth phase can be identified, that of remodeling into lamellar bone.

Osteolytic Phase. This phase begins with increased vascularity and cellularity in the marrow spaces. Almost immediately there is intense osteoclastic activity on the surfaces of bone trabeculae

(Fig 1A). These large osteoclasts lying in Howship's lacunae may have as many as 100 nuclei. As resorption of bone continues, there is an increase in fibrous tissue and vascularity becomes intense, with blood flow as much as 20 times that of normal. The adjacent fatty or hematopoietic marrow is replaced by fibrous tissue. In cancellous bone the trabeculae become slender and sparse, and in cortical bone large resorption cavities are seen. Concurrently with the osteoclastic activity, there is appositional new bone formation by prominent osteoblasts. Rapidly recurring cycles of bone resorption and new bone formation create the histologic picture of active pagetic bone.

Mixed Phase. Closely following the osteolytic phase is the mixed (or combined) phase, in which new bone formation predominates over resorption. Each new encroachment on the bone leaves a resorption line, part or all of which remains as a cement line when the new bone is deposited (Fig 1B). These lines and the intervening fragments of bone create the mosaic pattern that is characteristic of Paget's disease. The contiguous marrow spaces are

TABLE 2. REPORTED PATHOLOGIC FINDINGS IN SENSORINEURAL HEARING LOSS CAUSED BY PAGET'S DISEASE

<i>Pathologic Findings</i>	<i>No. of Ears</i>	<i>Authors</i>	<i>Year</i>	<i>Basis</i>
Hair cell loss	5	Rüedi ¹⁸	1968	Histologic
	2	Lindsay and Lehman ²¹	1969	Histologic
	4	Lindsay and Suga ²⁸	1976	Histologic
	5	Proops et al ¹⁹	1985	Histologic
	1	Friedmann ²²	1974	Histologic
Tectorial membrane atrophy	2	Lindsay and Lehman ²¹	1969	Histologic
Endolymphatic hydrops	1	Lindsay and Lehman ²¹	1969	Histologic
Arteriovenous vascular shunts	5	Rüedi ¹⁸	1968	Histologic
	1	Nager ¹	1975	Histologic
	1	Kelemen ²⁹	1977	Histologic
Stria vascularis atrophy	5	Kornfeld ¹⁷	1967	Histologic
	2	Davies ⁶	1968	Histologic
	9	Rüedi ¹⁸	1968	Histologic
	2	Lindsay and Lehman ²¹	1969	Histologic
Cochlear ossification	1	Goodhill ²⁷	1967	Radiographic
Internal auditory canal narrowing and/or lengthening	1	Mayer ¹¹	1917	Histologic
	1	Jenkins ⁷	1928	Speculation
	1	Nager and Mayer ¹²	1932	Speculation
	2	Griffey ¹⁶	1960	Histologic
	1	Gussen ²³	1970	Histologic
	1	Applebaum and Clemis ²⁰	1977	Histologic
Microneuromata	1	Wilson and Anson ¹⁵	1936	Histologic
	2	Nager ¹	1975	Histologic
	1	Lindsay and Suga ²⁸	1976	Histologic
	2	Proops et al ¹⁹	1985	Histologic
Microfractures		Numerous authors		Histologic

replaced by a fibrovascular connective tissue (Fig 1C).

Osteoblastic Phase. This is the "burnt-out" phase, which features dense irregular masses of pagetic bone with relatively little cellular activity and laid out in a prominent mosaic pattern (Fig 1D). The bone has no tendency to orient around vascular channels or to form haversian canal systems; therefore, it is relatively avascular.³⁴ The marrow is fibrous, with scattered telangiectatic vessels. Although there is increased bone mass, it is architecturally unsound and weak; presumably the cause is failure of the collagen fibers to be aligned along stress lines within each spicule of bone.

Lamellar Remodeled Phase. Skeletal bone normally undergoes a slow but constant remodeling process. In the temporal bone, areas of inactive osteoblastic pagetic bone may also undergo this process of remodeling into quite normal-appearing lamellar bone with distinct haversian canal systems. This phase is seen predominantly in mild asymptomatic Paget's disease and is only evident on histologic studies. The site of predilection for the remodeling phase is the posterior wall of the petrous bone, on which it forms bosses around the porus of the internal auditory canal (Fig 1E).

Often a single temporal bone shows different histologic phases in different sites in the bone. For example, 11 of the 26 temporal bones showed areas of both phase 3 (osteoblastic) and phase 4 (remodeled) pagetic bone (Table 3).

The normal human temporal bone consists of three layers. 1) The periosteal layer is composed of cancellous, solid, or trabeculated bone that makes up the squamous, tympanic, mastoid and most of the petrous bone. 2) The enchondral layer makes up most of the bony labyrinth and is distinctive in having islands of calcified cartilage known as globuli interossei. 3) The endosteal layer is a thin, compact layer of bone that lines the inner walls of the bony labyrinth.

Histologic studies show that Paget's disease first involves periosteal bone, and depending on the aggressiveness of the disease, it may extend into the enchondral layer and may finally invade the endosteal layer, in that sequence. Because of its potential for damaging inner ear function, we have graded Paget's disease according to its invasive behavior. Thus, in grade 1 (Fig 1E), only the periosteal layer is involved, in grade 2 the periosteal and enchondral layers are involved, and in grade 3 the periosteal, enchondral, and endosteal layers are involved (Fig 2A). In grading the 26 ears, we judged grade 1 in 4 ears, grade 2 in 8 ears, and grade 3 in 14 ears (Table 3).

CASE REPORTS

CASE 1

At the age of 23 years the patient was first noted to have Paget's disease of the lumbar spine and femur. At the age of 48 he experienced episodes of un-

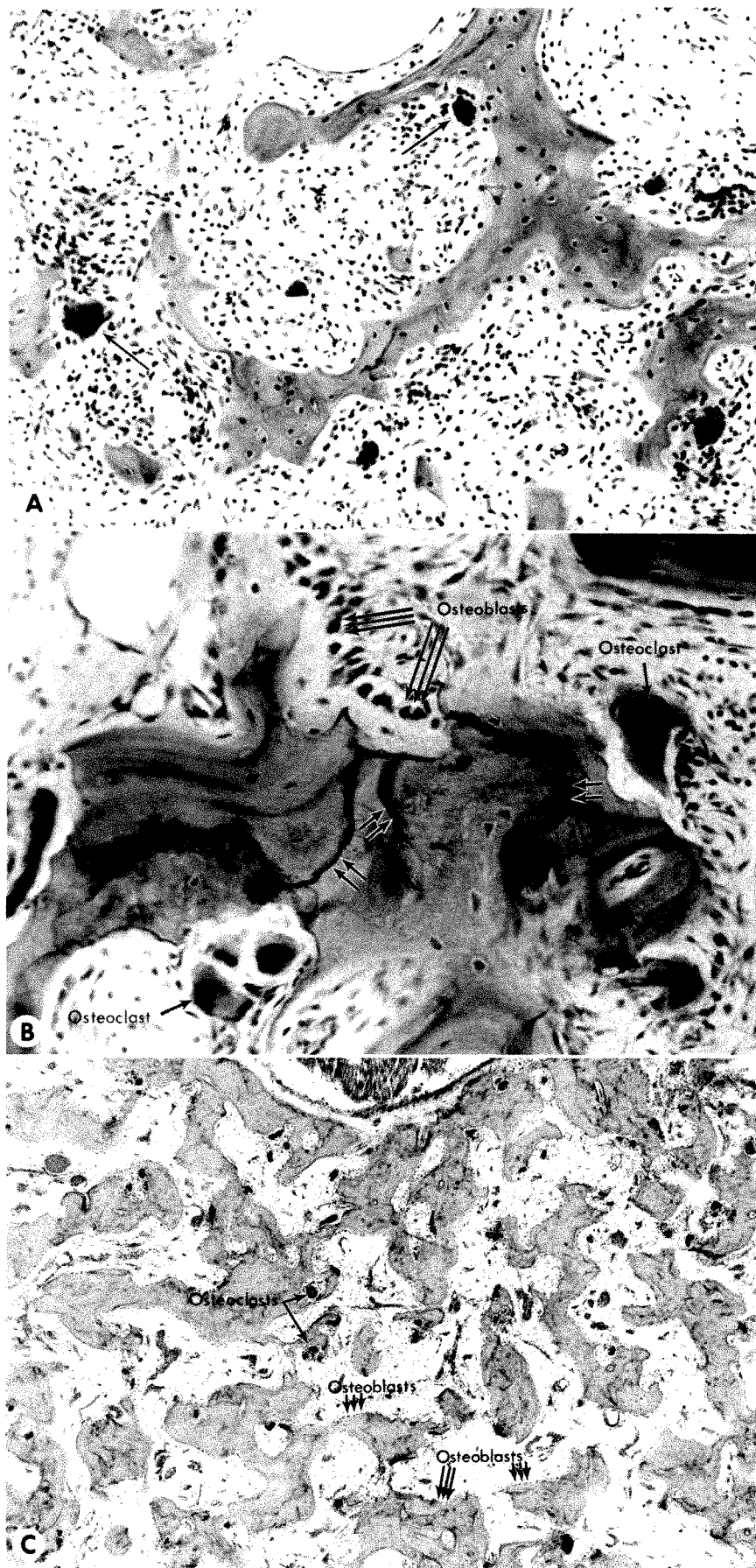
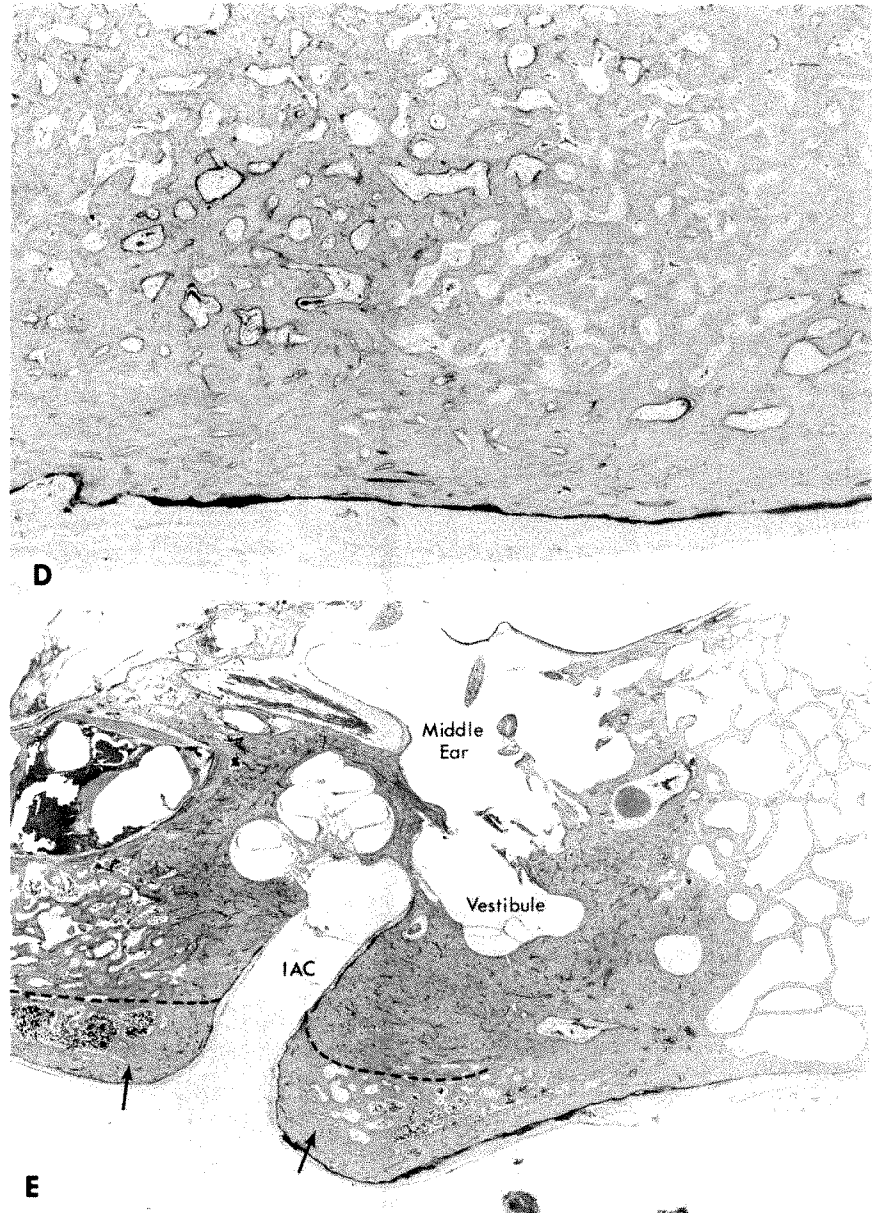


Fig 1. Four phases of pagetic bone changes. A) Phase 1, osteolytic phase, in woman, age 69 (original $\times 180$). Osteoclastic activity (arrows) is intense, and increase in vascularity can be seen. (Courtesy of F. Linthicum, House Ear Institute, Los Angeles, California.) B) (Case 15) Phase 2, mixed or combined phase, in woman, age 66 (original $\times 390$). Multiple cement lines (double arrows) can be seen and represent areas of bone resorbed and later replaced by osteoneogenesis. These cement lines may be seen long after disease has become inactive. C) (Case 5) Phase 2, mixed or combined phase, in woman, age 87 (original $\times 42$). In early stages of mixed phase of disease, marrow spaces are replaced by very vascular fibrous connective tissue. Numerous osteoclasts and osteoblasts are also seen. (Continued on next page.)

Fig 1 (continued). D) (Case 4) Phase 3, osteoblastic phase, in man, age 53 (original x19). Pagetic bony architecture is characteristically mosaic, with very little osteoblastic activity, no osteoclastic activity, and reduced vascularity. E) (Case 6) Phase 4, remodeled phase, in woman, age 96 (original x5). Pagetic bone undergoes process of remodeling into normal-appearing lamellar bone with distinct haversian canal systems. Spaces usually contain adipose tissue. Areas medial to interrupted lines (arrows) show bosses of pagetic bone that are in lamellar remodeled phase.



steadiness on rising from his chair. Caloric tests gave normal responses, and an audiogram revealed a mild sensorineural hearing loss with descending threshold patterns and a superimposed mild conductive loss on the right.

A hearing test at the age of 65 years showed a severe bilateral mixed hearing loss. Speech reception thresholds were 82 dB on the right and 84 dB on the left. Word discrimination scores were 60% on the right and 72% on the left. He died at the age of 70 years of multiple organ failure following fracture of a femur.

Histopathology. The pathologic findings in the two ears are nearly identical. There is thickening of the petrous pyramids by pagetic bone (Fig 2A). The histologic appearance is quite variable, showing in some areas a very dense, avascular bone with thick interlacing trabeculae and little fibrous tissue, and

in other areas a more lacy trabeculation separated by abundant, highly vascular loose connective tissue. Osteoclastic activity is seen in some areas.

The external auditory canals appear normal. The tympanic membranes show areas of fibrous thickening. The ossicles are of normal size and shape. In the right ear there is a small focus of pagetic bone in the superior margin of the footplate of the stapes, and the annular ligament has been replaced by a proliferation of dense fibrous tissue (Fig 2C). These changes would be consistent with fibrous fixation of the footplate. The tegmens of the middle ears and mastoids are thickened by pagetic bone, and the mastoid air cell systems are obliterated by a network of pagetic bone separated by an abundance of spaces containing fibrovascular tissue.

The internal auditory canals measure 3 mm in diameter and are within the range of normal (2 to 6

TABLE 3. DATA FOR 16 PATIENTS (26 EARS)

Ear	Case	Sex	Age	Side	Hearing Loss		Histologic Phase				Bone Grade
					Conductive	Sensorineural	1	2	3	4	
1	1	M	70	R	+	+		+	+		3
2				L	+	+		+	+		3
3	2	M	67	R	+	+		+	+		3
4				L	+	+		+	+		3
5	3	M	83	R	+	+		+	+		3
6				L	+	+		+	+		3
7	4	M	53	L	*	+			+	+	1
8	5	F	87	R	+	+		+			3
9				L	†	+		+			3
10	6	F	96	R		+			+	+	1
11				L	*	+			+	+	1
12	7	M	96	R		+				+	1
13	8	F	71	R	No audiogram				+	+	2
14				L	No audiogram				+	+	2
15	9	F	94	R	No audiogram				+	+	2
16				L	No audiogram				+	+	2
17	10	M	75	R	No audiogram				+		3
18				L	No audiogram				+		3
19	11	M	78	R	No audiogram				+	+	2
20	12	F	89	L	No audiogram				+	+	2
21	13	F	57	L	No audiogram				+	+	2
22	14	F	?	R	No audiogram			+	+		3
23				L	No audiogram			+	+		3
24	15	F	66	R	No audiogram			+			3
25				L	No audiogram			+			3
26	16	F	74	R	No audiogram			+	+	+	2

*Bone conduction thresholds not tested.

†Bone conduction thresholds not tested before age of 84. It is possible that, like opposite ear, this ear may have had conductive loss.

mm).³⁷ Over 90% of the enchondral bone has been replaced by pagetic bone. In the right ear there is a microfracture of the interscalar septum between the middle and apical turns and in the osseous spiral lamina of the basal turn. In both ears there are microfractures in the promontories of the cochlear walls with inward displacement of the inferior margins of the oval windows (Fig 2D). The round window niches are filled with thick interconnecting bands of fibrous tissue. A widening of the left posterior ampullary microfissure is filled with fibrous tissue (Fig 3A).

The hair cell population of the organ of Corti is normal in the right ear and diminished in the basal 9 mm of the left ear. There is patchy atrophy of the striae vasculares. The cochlear neuronal population is 18,864 on the right and 19,071 on the left (average normal count for the seventh decade is 22,900) (Figs 2B and 3B). The cochlear dendritic populations appear to parallel the soma (cell body) populations.

The utricular and saccular maculae and the cristae appear normal. There is partial loss of the dendritic fibers of the inferior divisions of the vestibular nerves; however, the superior divisions appear normal.

CASE 2

At the age of 37 this man was known to have Paget's disease of the skull, clavicle, ribs, spine, pel-

vis, and femur. He first complained of hearing loss at age 55. Audiometric studies showed a bilateral, mild, mixed hearing loss characterized by descending threshold patterns. Speech reception thresholds were 12 dB on the right and 14 dB on the left. Word discrimination scores were 92% for both ears. At the age of 59 an audiogram showed a progression of the hearing loss that was most severe on the left. An audiometric test at age 65 showed speech reception thresholds of 75 dB on the right and 60 dB on the left; word discrimination scores were 48% on the right and 68% on the left. He died at the age of 67 years of renal failure and congestive heart disease.

Histopathology. The pathologic findings in the two ears are nearly identical. There is mild diffuse pagetic enlargement of the petrous bones. The pagetic bone shows hypervascularity, an increased soft tissue-to-bone ratio, and numerous osteoclasts. These hyperactive areas are located principally around the internal auditory canals, the posterior walls of the petrous bones, and the petrous apices.

The external auditory canals appear normal. The ossicles show areas of fibrous tissue replacement of bone, but have normal size and shape and are not fixed. The internal auditory canals measure 7 mm in diameter, and in the right ear there is an exuberant growth of pagetic bone, extending from the anterior wall of the internal auditory canal, that has displaced the cochlear and vestibular nerves but does not appear to have caused pressure atrophy (Fig 4A).

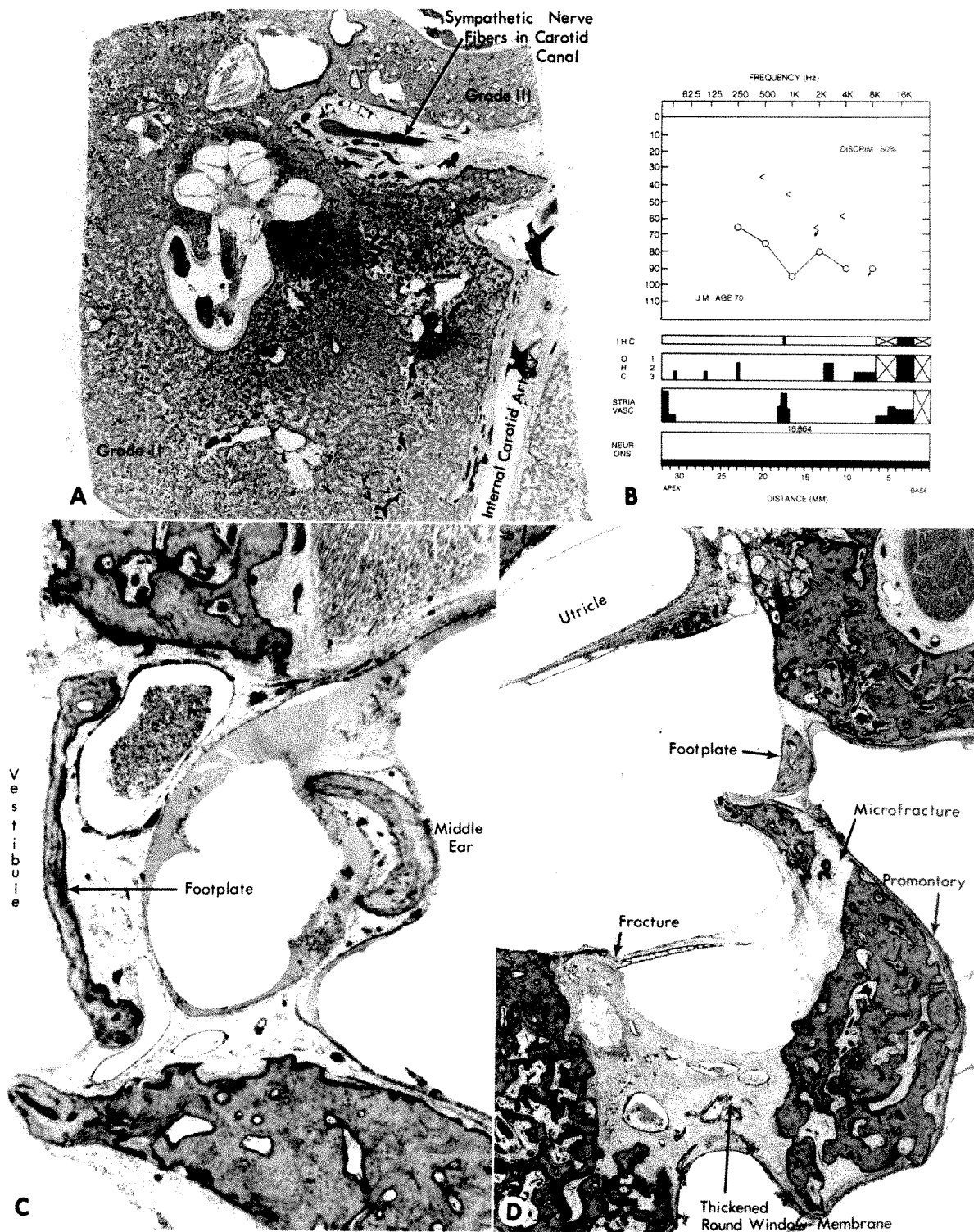


Fig 2. (Case 1) Right ear. A) Vertical section showing grade 3 pagetic involvement of temporal bone with marked thickening of petrous pyramid (original x3.5). B) Audiogram and cytochrome C histogram showing mixed hearing loss, minimal hair cell loss, and cochlear neuronal loss slightly greater than normal for age. Frequencies are plotted according to new database anatomic frequency scale (explained in text), and distance along cochlear duct is shown in millimeters from basal end. Black areas represent percentage loss for each structure studied. Neuronal counts were not segmentalized for this ear, because we had no normative data for vertical sections. Cross-hatched boxes indicate areas in which cellular differentiation was impossible because of angle of sectioning. IHC — inner hair cells, OHC — outer hair cells. C) Vertical section showing widening of oval window niche and laxity of annular ligament inferiorly (original x65). Superior part of annular ligament shows fibrotic changes. There is no bony encroachment on footplate or annular ligament. D) Vertical section showing microfracture extending from oval window niche to spiral ligament (original x24). It is filled with fibrous tissue. There is obliteration of round window niche by fibrous tissue, as well as fracture of osseous spiral lamina.

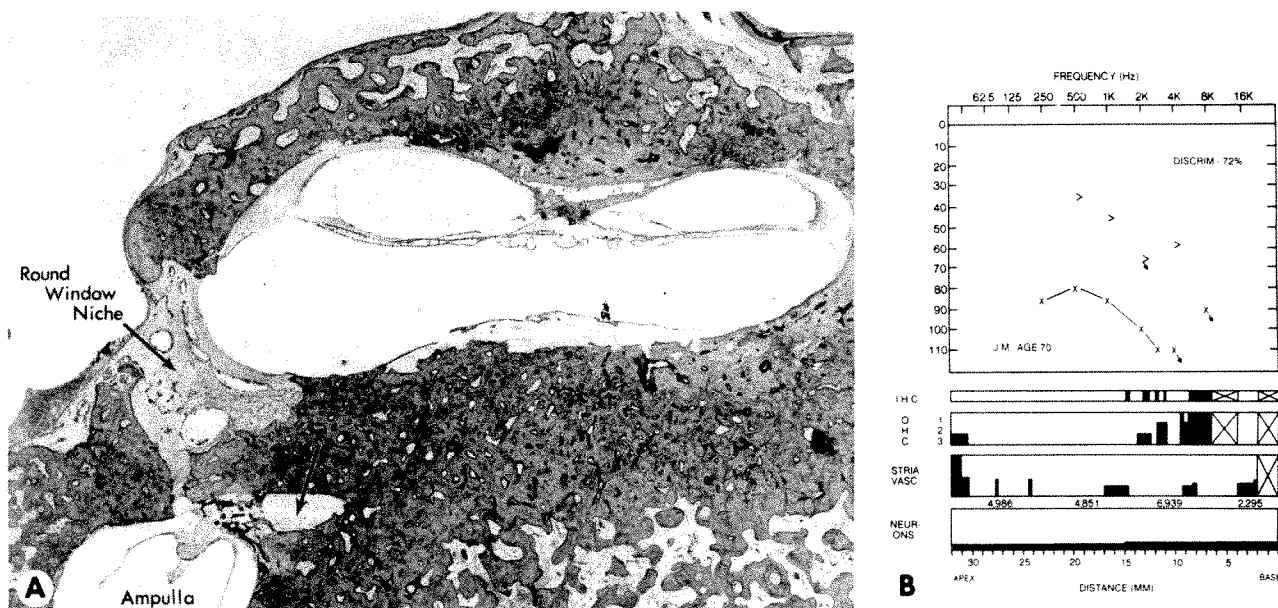


Fig 3. (Case 1) Left ear. A) Horizontal section showing partial obliteration of round window niche by fibrous tissue (original x15). There is widening and fibrosis of normally occurring microfissure between round window niche and posterior ampulla. There is partial atrophy of posterior ampullary nerve (arrow). B) Audiogram and cytochrome graph showing histologic findings similar to those of right ear. Neuronal counts are summed for each of four segments and have been compared to normal for age. Bone conduction responses could not be reliably attributed to either ear because of masking difficulties and may represent either one or both ears.

The organs of Corti and the spiral ligaments are normal. The striae vasculares show mild patchy atrophy, which appears normal for age. The cochlear neuronal population is 23,049 on the right and 23,463 on the left (average normal count for the seventh decade is 22,900) (Figs 4B and 5A). The dendritic populations appear to parallel the soma populations.

The vestibular sense organs appear normal, with

good populations of hair cells, and the vestibular nerves appear normal. In the left ear there are multiple microneuromas within the pagetic bone near the cribrose area for the superior division of the vestibular nerve (Fig 5B,C).

CASE 3

At the age of 83 years the patient was diagnosed as having Paget's disease of the skull, spine, pelvis,



Fig 4. (Case 2) Right ear. A) Spur of pagetic bone in internal auditory canal is impinging upon and displacing cochlear nerve (original x9). Internal auditory canal is widened to 7 mm and lengthened. Stapes footplate and saccule are normal, and endolymphatic duct (arrow) is patent. B) Audiogram and cytochrome graph showing mixed hearing loss and near-normal hair cell populations, stria vascularis, and cochlear neuronal counts.

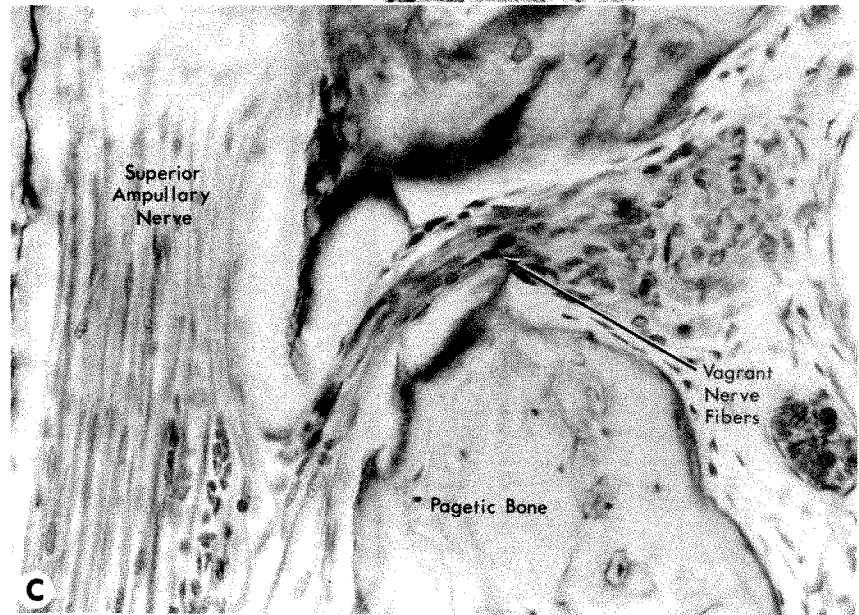
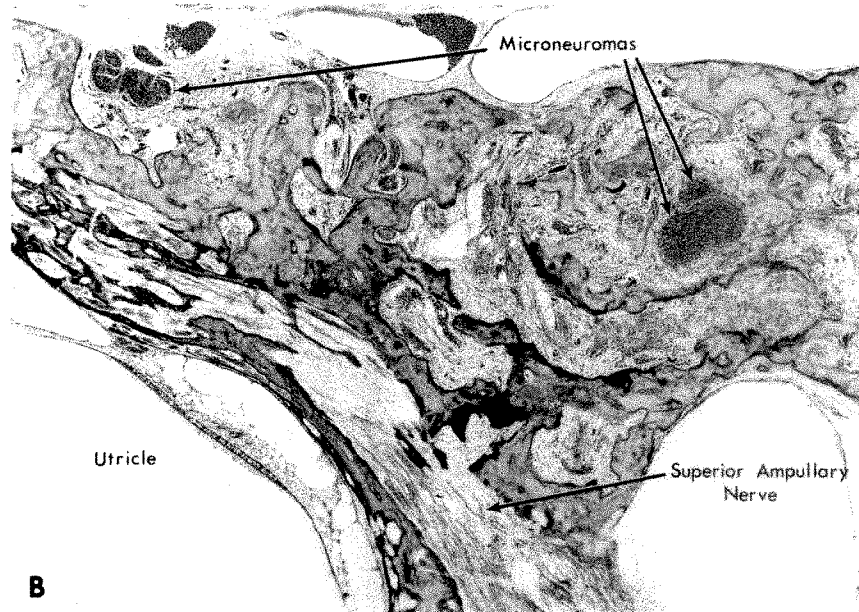
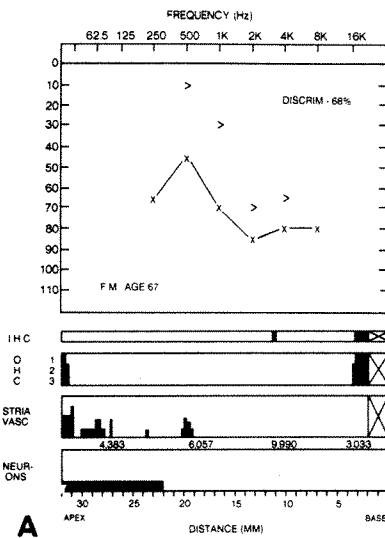


Fig 5. (Case 2) Left ear. A) Audiogram and cytochrome C histogram showing mixed hearing loss and histologic findings similar to those in right ear. B) Multiple microneuromas, presumably caused by blockage of cribrate areas by pagetic bone, causing injury to nerve fibers followed by vagrant regeneration (original x48). Superior ampullary nerve is atrophic (arrow). Utricular macula is normal. C) Nerve fiber bundle of main trunk of superior ampullary nerve is seen wandering into surrounding pagetic bone (original x510). When this vagrant nerve bundle was followed superiorly, it was found to enter large microneuroma seen in B.

clavicles, and scapulae. He first complained of hearing loss at the age of 78 years. An audiogram revealed a bilateral mixed hearing loss with air conduction thresholds in the 75-dB range and bone conduction thresholds at 30 dB for 500 and 1,000 Hz, with greater losses at higher frequencies. Word discrimination scores were 60% on the right and 40% on the left. He died 9 months later of pyelonephritis and cachexia.

Histopathology. The pathologic findings in the two ears are nearly identical. The external auditory canals, tympanic membranes, and ossicles appear normal. There is replacement of about 90% of the enchondral bone with pagetic bone. Thickening of the petrous bones has lengthened the internal auditory canals to 14 mm. The pagetic bone shows areas of increased vascularity, particularly in the petrous apices. There are foci of pagetic bone in the foot-

plates that are not causing fixation. There are scattered microfractures of the bony labyrinths, with particularly prominent ones in the promontories.

A patchy loss of hair cells is seen throughout both cochleas. The cochlear neuronal population is 12,336 on the right and 6,993 on the left (average normal count for the ninth decade is 18,700) (Fig 6A,B). The dendritic populations appear to parallel the soma populations (Fig 6C).

The vestibular sense organs appear normal. In the right ear microneuromas are seen in the ampullary branch of the superior division, the saccular nerve, and the posterior ampullary nerve.

CASE 4

Beginning in childhood, this patient suffered from type 1 neurofibromatosis. At the age of 49

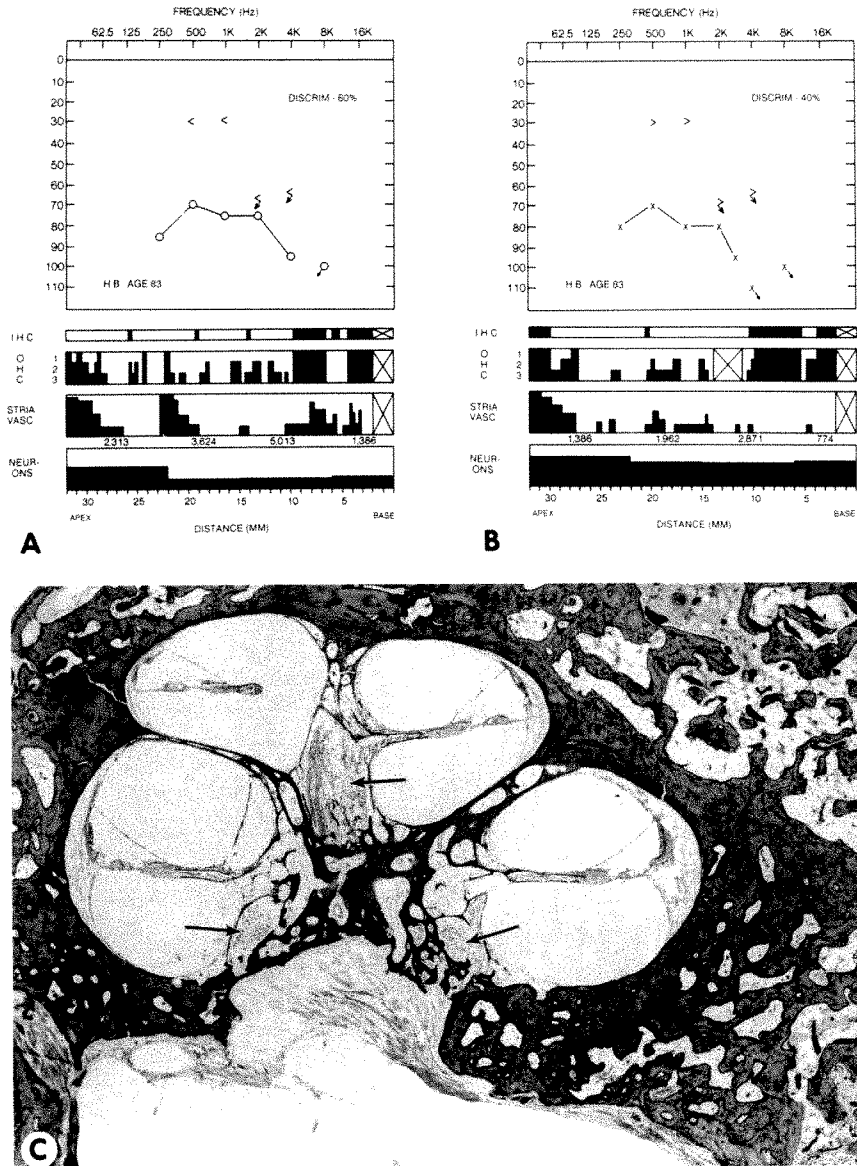


Fig 6. (Case 3) A) Right ear. Audiogram and cytochrome oxidase (CO) histochemistry showing mixed hearing loss and moderate cochlear neuronal loss when compared to normal for age. Moderate patchy hair cell and stria loss is also present. B) Left ear. Audiogram and cytochrome oxidase (CO) histochemistry showing mixed hearing loss as well as moderate hair cell loss and severe cochlear neuronal loss. Bone conduction responses could not be reliably attributed to either ear because of masking difficulties and may represent either one or both ears. C) Left ear (original x21). Photomicrograph of midmodiolar section of cochlea illustrating moderate to severe cochlear neuronal loss in all turns (arrows). Both axons and dendrites are decreased, indicative of primary neuronal degeneration related to aging (neural presbycusis). There is mild patchy atrophy of stria vascularis. Spiral ligament is normal for age.

years he had a sudden attack of vertigo associated with blurred vision, numbness and weakness of the left arm and face, and slurred speech, all of which persisted for several hours. He had a counterclockwise rotatory nystagmus and a partial right gaze palsy. Audiometric studies showed a mild bilateral high-tone sensorineural hearing loss. Word discrimination scores were 72% on the right and 68% on the left. There were no clinical manifestations of Paget's disease. He eventually became totally disabled from the neurofibromatosis and died at the age of 53 of coronary thrombosis.

Histopathology. Only the left temporal bone shows Paget's disease. The mastoid of this ear is the same size as the right, but has less pneumatic area because of pagetic thickening of the posterior wall. This thickened area contains dense trabeculae of lamellar bone with haversian canal systems separated by small islands of connective tissue. No areas of bone resorption are seen. No acoustic tumors are

present.

The organs of Corti are normal and the striae vasculares show mild atrophy. The cochlear neuronal population is 17,964 in the left, involved ear and 15,570 on the right (average normal count for the sixth decade is 27,100) (Fig 7). The dendritic populations appear to parallel the soma populations. The vestibular sense organs and nerves appear normal.

CASE 5

At the age of 80 years an audiogram showed a bilateral sensorineural hearing loss of 40 to 70 dB with a superimposed right conductive loss of 30 dB. Word discrimination scores were 68% on the right and 92% on the left.

At age 84 pure-tone testing showed thresholds of 80 dB on the right with 56% word discrimination and 80 to 100 dB on the left with zero word discrimination. She had a right-beating, direction-fixed,

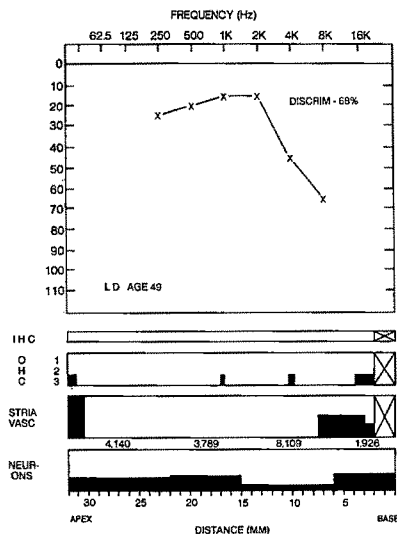


Fig 7. (Case 4) Left ear. Audiogram and cytochrome C histogram showing normal hair cell population but cochlear neuronal loss greater than normal for age. Bone conduction was not tested.

positional nystagmus. Caloric response was diminished on the left. Radiographic studies revealed Paget's disease of the skull. At the age of 87 years she had a cerebral infarct and died.

Histopathology. The pathologic findings in the two ears are nearly identical. The petrous pyramids are greatly enlarged by pagetic change that surrounds shells of remaining enchondral bone. The pagetic bone shows increased vascularity and active osteoclastic as well as osteoblastic activity. The tympanic membranes are thickened by fibrous proliferation of the lamina propria. The mallei and incudes are normal. The oval windows are narrowed slightly, but the stapes footplates are not impacted or ankylosed (Fig 8A). The round windows are slightly narrowed but not obliterated. There are microfractures through the promontories, extending into the round window niches and the scalae tympani of the basal turns. The widest diameters of the internal auditory canals measure 2.5 mm; however, the nerve trunks do not appear to be compressed (Fig 9A).

Hair cells can be identified throughout the organs of Corti. There is mild scattered atrophy of the striae vasculares. The cochlear neuronal population is 6,741 on the right and 12,240 on the left (average normal count for the ninth decade is 18,700) (Figs 8B and 9B). The dendritic population appears to parallel the cell body population.

The vestibular labyrinths are slightly collapsed. The vestibular dendrites appear to be reduced in number. The hair cell populations of the vestibular sense organs appear to be normal.

CASE 6

At the age of 92 this woman was noted to have a hearing loss. Audiometric tests revealed a bilateral,

nearly symmetric sensorineural hearing loss characterized by descending thresholds beginning at 25 dB for 250 Hz and progressing to 90 dB for 8 kHz. Word discrimination scores were 20% in both ears. She was noted to have hypertension and Paget's disease of the skull, and had suffered several strokes. At the age of 95 it was recorded that she had a gradual decline in mental and physical health. At age 96 she fell and fractured her left wrist and shoulder and died soon thereafter.

Histopathology. The pathologic findings in the two ears are nearly identical. The tympanic membranes, ossicles, petrous apices, and mastoids appear normal. There are pagetic bony protuberances of the posterior walls of the petrous bones, principally around the internal auditory canals and more severe on the right side. The superior and the anterior margins of the meatus are overlapped by pagetic bone. The protuberances consist of normal-appearing lamellar bone and islands of healthy marrow. It appears that these protuberances are remodeled, healed pagetic bone (Fig 1E).

There is a near-total loss of the organs of Corti in the basal 12 mm of the cochleas. In these areas both the inner and outer hair cells are missing and the organ of Corti is atrophied, with loss of pillar cells. The tectorial membranes are missing in the 0- to 8-mm regions. The cochlear neuronal population is 16,268 on the right and 15,831 on the left (average normal count for the 10th decade is 16,600). The dendritic populations parallel the soma populations. The striae vasculares show atrophy that is most severe in the apical regions (Fig 10). The vestibular sensory and neural structures appear normal.

CASE 7

At the age of 65 this man experienced a sudden hearing loss in his left ear. Audiometric tests at the age of 96 showed a moderately severe sensorineural hearing loss on the right with 54% word discrimination, and a profound hearing loss on the left. He showed no clinical evidence of Paget's disease. He died of pneumonia at age 96. On histologic studies, both temporal bones show areas of phase 4 Paget's disease (lamellar remodeling) in the periosteal bone (grade 1) of the petrous apices and mastoids and around the internal auditory canals. It is quite improbable that the grade 1 Paget's disease in these ears had any effect on hearing. The right cochlea shows scattered areas of hair cell loss and patchy stria atrophy compatible with presbycusis and a neuronal population of 14,562 (average neuronal count for the 10th decade is 16,600) (Fig 11). The left cochlea shows severe cochleosaccular degeneration compatible with the pathologic findings reported for sudden hearing loss.³⁸

In the right ear the maculae, cristae, and inferior division of the vestibular nerve are normal. There is

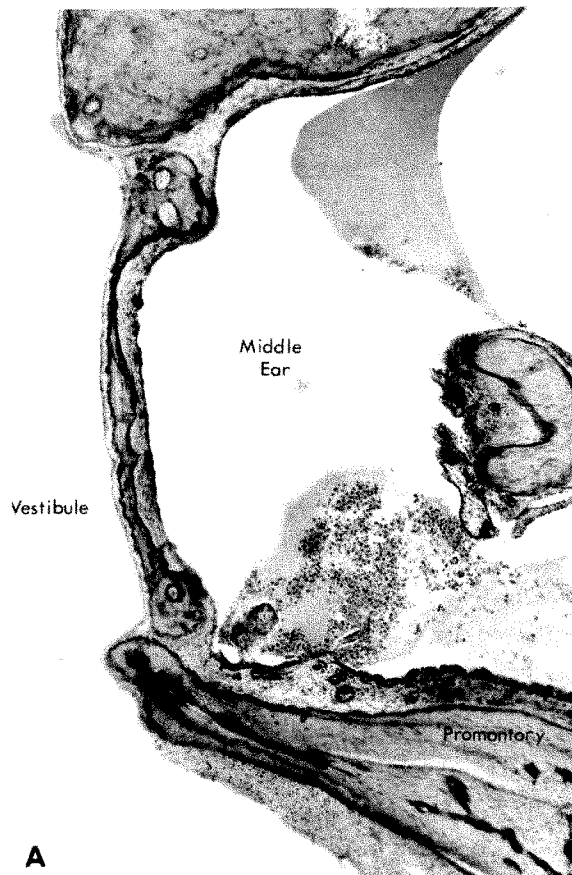
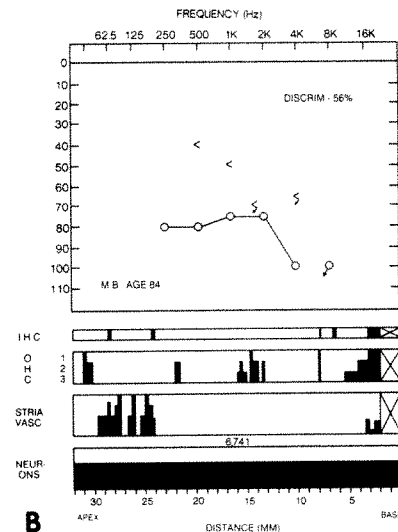


Fig 8. (Case 5) Right ear. A) Vertical section through stapes footplate shows oval window that is narrowed slightly, but footplate is neither impacted nor ankylosed (original $\times 81$). B) Audiogram and cytochromeogram showing mixed hearing loss, scattered mild hair cell loss, and severe cochlear neuronal loss. Neuronal counts were not segmentalized, because we had no normative data for vertical sections.



a 40% loss of neurons in the superior division of the vestibular nerve.

In the remaining 14 temporal bones from nine cases without audiometric data the pathologic changes are similar to those in the 12 bones already described. None of these ears show blockage of the external auditory canals, ossicular fixation, or obliteration of the round window niches. Five have cochlear neuronal losses greater than normal for age. Twelve have stria atrophy consistent with normal for age. The hair cell losses in these ears are mild and are presumed to be due to aging.

DISCUSSION

Audiograms are available on 12 of the 26 ears, with 7 (58%) showing mixed losses and 5 (42%) showing only sensorineural losses. The threshold patterns are descending for bone conduction, and the 7 ears with mixed hearing losses show flat air conduction thresholds; thus, the bone conduction and air conduction curves approximate each other at the high frequencies. There is, therefore, a progressively decreasing magnitude of conductive loss from low to high frequencies that is characteristic of stiffness lesions (as opposed to mass lesions) of the sound transmission system.

Comparing the hearing losses in these 12 pagetic ears with the normative data of Glorig and Davis³⁹ and Spoor,⁴⁰ the pagetic ears showed greater losses,

especially in the lower frequencies. When Moller's⁴¹ data for 70- and 75-year-olds are used, 10 of 11 ears had more severe losses than normal (the patient in case 4 had his audiogram at age 49, for which Moller did not have age-matched data). Compared to Plomp's⁴² data for average hearing loss in the better ear, all seven patients fell outside the 85th-percentile category, and four outside the 95th-percentile group of the standard population. Moreover, when the data for better and worse ear averages (average for 0.5, 1, 2, and 4 kHz) in the 12 ears were compared to the National Study of Hearing pilot study group data presented by Davis,⁴³ 10 of 12 ears had worse averages than the mean plus two standard deviations for age-matched normal subjects. The hearing losses of Paget's disease, therefore, are greater than those of age-matched control subjects.

Having shown that a conductive hearing loss occurs more commonly in Paget's disease, and that a sensorineural hearing loss occurs that is greater than expected for age, the challenge is to identify pathologic correlates to explain these hearing losses.

We cannot find an adequate explanation for conductive hearing loss in the 26 ears studied. The external auditory canals show a tendency to slight narrowing, and two ears show moderate fibrous thickening of their tympanic membranes. The ossicles are intact, and none show osseous fixation.

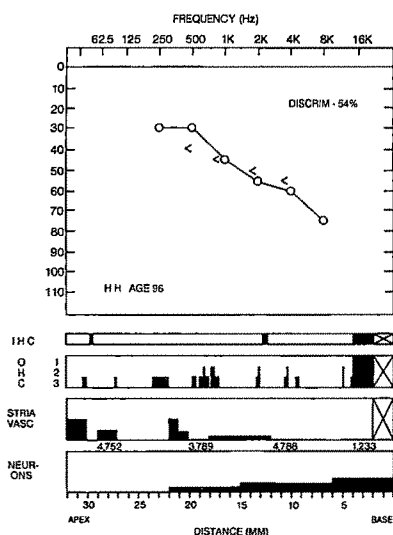


Fig 11. (Case 7) Right ear. Audiogram shows descending threshold pattern. There is mild scattered outer hair cell loss, mild patchy stria atrophy, and slight neuronal loss in basal turn.

hearing losses. The pagetic ears with excessive hearing losses show no correlation of pure-tone threshold elevation with either the severity or location of hair cell losses. In the study of cochlear neurons, the objective is to assess the extent of deafferentation of the organ of Corti. Such assessments can be done by counting cochlear neuronal cell bodies and by making visual judgments as to the amount of dendritic innervation. In these pagetic ears the dendritic populations seemed to parallel the neuronal counts. In 5 of 12 (42%) ears the neuronal losses were at least 25% greater than the average for age (Table 4). It is doubtful, however, that the loss of cochlear neurons is related to the elevation of pure-tone bone conduction thresholds. Animal experiments⁴⁹ have shown that loss of neurons correlates poorly with pure-tone thresholds. Human studies,⁵⁰ however, have shown a direct relationship of neuronal loss to loss of word discrimination.

It has been shown that atrophy of the stria vascularis correlates directly with elevation of pure-tone thresholds,⁵¹ and furthermore, when stria atrophy occurs in isolation, it causes flat audiometric threshold patterns. In the pagetic ears, however, the extent of stria atrophy is generally mild and consistent with age, and the audiometric thresholds for bone conduction were descending rather than flat, with some showing sharp drops between 1 and 2 or 2 and 4 kHz. None of the ears showed any significant changes in the spiral ligaments, tectorial membranes, or limbi. The pagetic bone had not encroached on the cochlear nerve trunks or invaded the modioli or inner ears.

The presence of microfractures in the bony labyrinths is indicative of the physical stresses that accompany the changing mass and density of bone in this disease. It is not clear whether these microfractures begin as fissures that gradually widen with

TABLE 4. PERCENTAGE DEVIATION OF COCHLEAR NEURONAL COUNTS FROM AVERAGE NORMAL COUNT FOR AGE

Case	Age	Ear	Neuronal Population	Normal for Age	Deviation
1	70	R	18,864	22,900	-18%
		L	19,071	22,900	-17%
2	67	R	23,049	22,900	+1%
		L	23,463	22,900	+2%
3	83	R	12,336	18,700	-34%
		L	6,993	18,700	-63%
4	53	L	17,964	25,000	-28%
5	87	R	6,741	18,700	-64%
		L	12,240	18,700	-35%
6	96	R	16,268	16,600	-2%
		L	15,831	16,600	-5%
7	96	R	14,562	16,600	-12%

time or whether they occur suddenly and possibly create temporary perilymphatic fistulas. In the latter case, they might be expected to cause sudden vertigo and hearing loss, but such symptoms were not recorded in our patients with microfractures. All microfractures are solidly sealed by a combination of fibrous proliferation and an unknown type of homogeneous ground substance.

Vertigo was recorded in 4 of the total group of 16 subjects (Table 5⁵²⁻⁵⁴). The symptoms could be characterized as episodes of motion-induced unsteadiness that is similar to a type of dysequilibrium of aging (J. B. Nadol, Jr, and H. F. Schuknecht, unpublished observations, 1989). Except for one case, there were no degenerative changes such as loss of hair cells that could be detected in the maculae or cristae. Losses of vestibular nerve fibers greater than normal for age occurred in nine ears of six subjects, of whom three had a history of vertigo and three did not. The losses occurred only in the superior division in three ears, only in the inferior division in three ears, and in both divisions in three ears. Three ears from three subjects had evidence of partial to total atelectasis of the saccular, utricular and ampullary, and ampullary walls, respectively. Two of these subjects had a history of vertigo. Microneuromas of the vestibular nerves were present in four ears of three subjects, none of whom had a history of vertigo. In two of the above three subjects, the opposite ear showed vagrant migration of the vestibular nerves without microneuroma formation.

A calcium-lowering and phosphate-lowering hormone, calcitonin, was discovered by Copp et al⁵⁵ in 1962 and was viewed as a major calcium-regulating factor. Its role in human physiology remains controversial; however, it appears to be useful in the treatment of Paget's disease.⁵⁶ Calcitonin has been shown to inhibit osteoclastic activity and to lower serum calcium levels. Calcitonin has been reported to relieve bone pain, decrease excessive cardiac output, and to stabilize hearing.⁵⁷ Three subjects in this series received calcitonin for various durations, but

TABLE 5. VESTIBULAR SYMPTOMS AND PATHOLOGIC CHANGES

Ear	Case	Ver- tigo	Side	Vestib- ular Atelec- tasis*	Nerve Fiber Loss		Mi- cro- frac- tures†	Mi- cro- neu- roma
					Sup	Inf		
1	1	+	R			+	+	
2			L			+	+	
3	2		R					
4			L					+
5	3		R		+	+	+	+
6			L				+	
7	4	+	L	+	(S)			
8	5	+	R		+	+	+	
9			L	+	(U/A)	+	+	
10	6		R				+	
11			L				+	
12	7	+	R		+			
13	8		R		+			
14			L		+			
15	9		R					
16			L					
17	10		R				+	
18			L	+	(A)			
19	11		R					
20	12		L					
21	13		L					
22	14		R					
23			L				+	
24	15		R	§		+	+	+
25			L				+	+
26	16		R					

S — saccular wall collapse only, U/A — utricular and ampullary wall collapse, A — ampullary wall collapse only.

*Defined in Merchant and Schuknecht.⁵²

†Different from microfissures described in normal adult human temporal bone.^{53,54}

§Although no vestibular atelectasis is noted, there is moderate loss of sensory hair cells in posterior canal crista ampullaris.

longitudinal audiometric studies in these subjects are not available.

Diphosphonate compounds have also shown benefits biochemically, radiographically, and clinically. Both diphosphonates and calcitonins shift the state of the high bone turnover to that of a lower turnover in which resorption and new bone deposition are still apparently geared to each other. The collagen fibers are thus deposited in a more orderly, parallel arrangement.⁵⁸

Having failed to identify specific pathologic cor-

relates for the conductive and sensorineural hearing losses, we suspect that impairment of compliancy of these systems may be the cause. The highly tuned middle and inner ear mechanisms could be altered by the changes in the density, mass, and form of the middle and inner ear bony structures that occur in Paget's disease. The frequency of microfractures attests to the stresses that develop within the bony labyrinth.

CONCLUSIONS

1. Paget's disease of the temporal bone frequently causes conductive hearing loss as well as sensorineural loss that is greater than normal for age.
2. The histologic features of Paget's disease of the temporal bone are similar to those lesions occurring elsewhere in the skeleton, but in addition to osteolytic, mixed, and osteoblastic phases, a fourth phase, that of lamellar remodeling, can be identified.
3. The pagetic lesion was present in the periosteal layer in all 26 temporal bones, extended to the enchondral layer in 22, and additionally involved the endosteal layer in 14.
4. Contrary to common opinion, the conductive hearing loss is not caused by ossicular fixation; in fact, no cause could be identified in the seven ears with documented conductive hearing losses.
5. In none of the 26 temporal bones have the pagetic lesions invaded the inner ear spaces or compressed the nerve trunks in the internal auditory canals.
6. Even though all 26 cochleas showed presbycusis changes, including loss of hair cells and neurons and atrophy of the striae vasculares, there were no pathologic changes in these structures that could be directly attributed to Paget's disease.
7. The occasional occurrence of microfractures of the bony labyrinth attests to the considerable stresses that develop as the pagetic bone replaces normal bone.
8. We conclude that both the conductive and sensorineural components of the hearing loss in Paget's disease are caused by changes in bone density, mass, and form that dampen the finely tuned motion mechanics of the middle and inner ears.

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REFERENCES

1. Nager GT. Paget's disease of the temporal bone. *Ann Otol Rhinol Laryngol* 1975;84(suppl 22).
2. Lindsay JR, Perlman HB. Paget's disease and deafness. *Arch Otolaryngol* 1936;23:580-7.
3. Fowler EP. Etiological and clinical types of so-called nerve deafness. *Laryngoscope* 1937;47:586-93.
4. Clemis JD, Boyles J, Harford ER, Petasnick JP. The clinical diagnosis of Paget's disease of the temporal bone. *Ann Otol Rhinol Laryngol* 1967;76:611-23.
5. Davies DG. Paget's disease of the temporal bone. A clinical and histopathological survey. *Acta Otolaryngol [Suppl]* (Stockh) 1968(suppl 242).
6. Harner SG, Rose DE, Facer GW. Paget's disease and hearing loss. *Otolaryngology* 1978;86:869-74.
7. Jenkins GJ. A pathological and clinical comparison. *Otosclerosis*. *J Laryngol Otol* 1928;43:1-14.
8. Barth H. Klinische Befunde am Hör und Gleichgewichtsapparat bei den metapoetischen Knochenerkrankungen. *Z Hals*

Nasen Ohrenheilkd 1934;35:305-24.

9. Petasnick JP. Tomography of the temporal bone in Paget's disease. *Am J Roentgenol* 1969;105:838-43.

10. Tamari M. Histopathologic changes of the temporal bone in Paget's disease. *Ann Otol Rhinol Laryngol* 1942;51:170-208.

11. Mayer O. Untersuchungen über die Otosklerose. Wien: Alfred Hölder, 1917:74-113.

12. Nager FR, Meyer M. Die Erkrankungen des Knochensystems und ihre Erscheinungen an der Innenhorkapsel des Menschen. Berlin: S Karger, 1932:124.

13. Rosenkrantz JA, Wolf J, Kaicher JJ. Paget's disease (osteitis deformans). Review of one hundred eleven cases. *Arch Intern Med* 1952;90:610-33.

14. Sparrow NL, Duvall AJ III. Hearing loss and Paget's disease. *J Laryngol Otol* 1967;81:601-11.

15. Wilson JG, Anson BJ. Histologic changes in the temporal bone in osteitis deformans (Paget's disease). *Arch Otolaryngol* 1936;23:57-77.

16. Griffey LE. The temporal bone in Paget's disease. *Ann Otol Rhinol Laryngol* 1960;69:178-83.

17. Kornfeld M. Pathological changes in the stria vascularis in Paget's disease. *Pract Otorhinolaryngol* 1967;29:406-32.

18. Ruedi L. Are there cochlear shunts in Paget's and Recklinghausen's disease? *Acta Otolaryngol (Stockh)* 1968;65:13-24.

19. Proops D, Bayley D, Hawke M. Paget's disease and the temporal bone — a clinical and histopathological review of six temporal bones. *J Otolaryngol* 1985;14:20-9.

20. Applebaum EL, Clemis JD. Temporal bone histopathology of Paget's disease with sensorineural hearing loss and narrowing of the internal auditory canal. *Laryngoscope* 1977;87:1753-9.

21. Lindsay JR, Lehman RH. Histopathology of the temporal bone in advanced Paget's disease. *Laryngoscope* 1969;79:213-27.

22. Friedmann I. Pathology of the ear. Oxford, England: Blackwell Scientific Publications, 1974:229-33.

23. Gussen R. Early Paget's disease of the labyrinthine capsule. Case report and bone study. *Arch Otolaryngol* 1970;91:341-5.

24. Mayer O. The pathology of otosclerosis. *J Laryngol Otol* 1928;43:843-51.

25. Goodhill V. Pseudo-otosclerosis. *Laryngoscope* 1960;70:722-57.

26. Waltner JC. Stapedectomy in Paget's disease. Histological and clinical studies. *Arch Otolaryngol* 1965;82:355-8.

27. Goodhill V. In discussion: Clemis JD, Boyles J, Harford ER, Petasnick JP. The clinical diagnosis of Paget's disease of the temporal bone. *Trans Am Otol Soc Inc* 1967;55:188-203.

28. Lindsay JR, Suga F. Paget's disease and sensori-neural deafness: temporal bone histopathology of Paget's disease. *Laryngoscope* 1976;86:1029-42.

29. Kelemen G. Temporal bone showing otosclerosis, Paget's disease and adenocarcinoma. *Ann Otol Rhinol Laryngol* 1977;86:381-5.

30. Guild SR. A graphic reconstruction method for the study of the organ of Corti. *Anat Rec* 1921;22:141-57.

31. Schuknecht HF. Techniques for study of cochlear function and pathology in experimental animals. Development of the anatomical frequency scale for the cat. *Arch Otolaryngol* 1953;58:377-97.

32. Otte J, Schuknecht HF, Kerr AG. Ganglion cell populations in normal and pathological human cochleae. Implications for cochlear implantation. *Laryngoscope* 1978;88:1231-46.

33. Suzuka Y, Schuknecht HF. Retrograde cochlear neuronal degeneration in human subjects. *Acta Otolaryngol [Suppl] (Stockh)* 1988(suppl 540).

34. Singer FR, Schiller AL, Pyle EB, Krane SM. Paget's disease of bone. In: Avioli LV, Krane SM, eds. *Metabolic bone disease*. Vol 2. New York, NY: Academic Press, 1978:489-575.

35. Jaffe HL. Paget's disease. In: *Metabolic, degenerative, and inflammatory diseases of bones and joints*. Philadelphia, Pa: Lea & Febiger, 1972:240-71.

36. Bullough PG, Vigorita VJ. Atlas of orthopaedic pathology with clinical and radiologic correlations. New York, NY: Gower Medical Publishing, 1984:3.15-3.21.

37. Pérez Olivares F, Schuknecht HF. Width of the internal auditory canal. A histological study. *Ann Otol Rhinol Laryngol* 1979;88:316-23.

38. Schuknecht HF, Donovan ED. The pathology of idiopathic sudden sensorineural hearing loss. *Arch Otorhinolaryngol* 1986;243:1-15.

39. Glogic A, Davis H. Age, noise and hearing loss. *Ann Otol Rhinol Laryngol* 1961;70:556-71.

40. Spoor A. Presbycusis values in relation to noise induced hearing loss. *Int Audiol* 1967;6:48-57.

41. Moller MB. Changes in hearing measures with increasing age. In: Hinchcliffe R, ed. *Hearing and balance in the elderly*. London, England: Churchill Livingstone, 1983:97-122.

42. Plomp R. Auditory handicap of hearing impairment and the limited benefit of hearing aids. *J Acoust Soc Am* 1978;63:533-49.

43. Davis A. The epidemiology of hearing disorders. In: Hinchcliffe R, ed. *Hearing and balance in the elderly*. London, England: Churchill Livingstone, 1983:1-43.

44. Lynch TJ. Signal processing by the cat middle ear. Admittance and transmission, measurements and models [Thesis]. Cambridge, Mass: Massachusetts Institute of Technology, 1981.

45. Etholm B, Belal A Jr. Senile changes in the middle ear joints. *Ann Otol Rhinol Laryngol* 1974;83:49-54.

46. Elpern BS, Greisen O, Andersen HC. Experimental studies on sound transmission in the human ear. VI. Clinical and experimental observations on non-otosclerotic ossicle fixation. *Acta Otolaryngol (Stockh)* 1965;60:223-30.

47. McElveen JT, Goode RL, Miller C, Falk SA. Effect of mastoid cavity modification on middle ear sound transmission. *Ann Otol Rhinol Laryngol* 1982;91:526-32.

48. Harty M. Elastic tissue in the middle-ear cavity. *J Laryngol Otol* 1953;67:723-9.

49. Schuknecht HF. Pathology of the ear. Cambridge, Mass: Harvard University Press, 1974.

50. Pauler M, Schuknecht HF, Thornton AR. Correlative studies of cochlear neuronal loss with speech discrimination and pure-tone thresholds. *Arch Otorhinolaryngol* 1986;243:200-6.

51. Pauler M, Schuknecht HF, White JA. Atrophy of the stria vascularis as a cause of sensorineural hearing loss. *Laryngoscope* 1988;98:754-9.

52. Merchant SN, Schuknecht HF. Vestibular atelectasis. *Ann Otol Rhinol Laryngol* 1988;97:565-76.

53. Mayer O. Über ihre Entstehung der Spontanfrakturen des Labyrinthkapsel und ihre Bedeutung für die Otosklerose. *Z Hals Nasen Ohrenheilkd* 1930;26:261-79.

54. Harada T, Sando I, Meyers EN. Microfissure in the oval window area. *Ann Otol Rhinol Laryngol* 1981;90:174-80.

55. Copp DH, Cameron EC, Cheney BA, Davidson AGF, Henze KG. Evidence for calcitonin — a new hormone from the parathyroid that lowers blood calcium. *Endocrinology* 1962;70:638-49.

56. Austin LA, Heath H III. Calcitonin. Physiology and pathophysiology. *N Engl J Med* 1981;304:269-78.

57. El Sammaa M, Linthicum FH Jr, House HP, House JW. Calcitonin as treatment for hearing loss in Paget's disease. *Am J Otol* 1986;7:241-3.

58. Krane SM. Paget's disease of bone. In: Braunwald E, Isselbacher KJ, Petersdorf RF, Wilson JD, Martin JB, Fauci MS, eds. *Harrison's Principles of internal medicine*. 11th ed. New York, NY: McGraw-Hill, 1987:1900-2.

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GLEN K. MARTIN, PhD

LAURIE A. OHLMS, MD

FRANCES P. HARRIS, PhD

DANIEL J. FRANKLIN, MD

BRENDA L. LONSBURY-MARTIN, PhD

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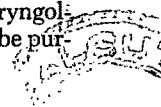
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From the Department of Otorhinolaryngology and Communicative Sciences, Baylor College of Medicine, Houston, Texas. Supported in part by funds from the Public Health Service (NS 10940, NS 22278, NS 27247, ES 03500) and the Deafness Research Foundation to Baylor College of Medicine.

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BRENDA L. LONSBURY-MARTIN, PhD

FRANCES P. HARRIS, PhD

MARGARET D. HAWKINS

BARDEN B. STAGNER

GLEN K. MARTIN, PhD

HOUSTON, TEXAS

Distortion product otoacoustic emissions (DPEs) at the $2f_1 - f_2$ frequency were recorded from 44 normal ears in response to equilevel primary tones. Detailed testing included the recording of DPE "audiograms" in 100-Hz steps from 1 to 8 kHz at three primary-tone levels (65, 75, and 85 dB sound pressure level [SPL]). In addition, response-growth or input-output (I/O) functions depicting the relationship of the amplitudes of DPEs to primary-tone levels, ranging from 25 to 85 dB SPL in 5-dB steps, were also tested for 11 frequencies distributed at quarter-octave intervals over the identical frequency range. The average DPE "audiogram" illustrating the frequency response of these emissions demonstrated a bilobed contour having a low-frequency maximum at approximately 1.5 kHz and a high-frequency peak that plateaued at about 5.5 kHz. The two maximum regions were separated by a minimum around 2.5 kHz. Depending on the frequency region, the average I/O functions exhibited detection "thresholds" at 3 dB above the noise floor at primary levels between 35 and 45 dB sound pressure level. The dynamic range of the emitted response between detection "threshold" and maximum amplitude varied over a 40-dB extent of the stimulus-level dimension. Approximately one third of the ears exhibited irregular DPE "audiograms" in which emitted responses were significantly reduced in restricted regions tested by low, medium, or high frequencies. When the 44 ears were separated into two groups representing more-normal and less-normal responses, the irregular "normal" ears demonstrated increased variability, especially in high-frequency regions. Mean age did not explain the differences noted between the two types of normally hearing subjects. However, across ears, DPE amplitudes and "thresholds" for the highest frequencies tested were correlated significantly with age in that the oldest individuals showed higher "thresholds" and lower amplitudes.

KEY WORDS — audiograms, human distortion product emissions, response-growth functions.

INTRODUCTION

Otoacoustic emissions (OAEs) represent a class of cochlear response that was discovered in relatively recent times.¹ On the basis of the results of a number of investigations of these responses and their relation to behavioral hearing, the notion has emerged that OAEs represent some aspect of the mechanism responsible for the high sensitivity and sharp tuning exhibited by the human ear. In particular, Kemp² has proposed that a biomechanical amplifier within the organ of Corti underlies these properties. This amplifier is the origin of OAEs that are apparently generated as a by-product of the traveling wave-initiated amplitude enhancement of basilar membrane vibration. In particular, two types of evoked emissions can be distinguished on the basis of the latency of the emitted response with respect to stimulus onset. One type, referred to by Zwicker³ as "delayed" evoked OAEs because of their typical occurrence following the stimulus, consists of two subtypes: the transiently evoked otoacoustic emissions (TEOAEs) and the stimulus frequency otoacoustic emissions (SFEs). These delayed evoked emissions appear to arise from specific impedance discontinuities within a given cochlea. Energy reflected from these idiosyncratic sites results in a unique emission pattern from every cochlea. Another type of evoked OAE, which typically occurs instantaneously with acoustic stimulation in contrast to the more latent TEOAEs and SFEs, is referred to as a distortion product otoacoustic emission (DPE). The DPEs seem to represent energy escape² resulting

from the basilar membrane's inability to respond to two stimuli simultaneously. Because this property is continuously distributed along the basilar membrane, DPEs can be generated at any frequency by selection of the appropriate eliciting tones.

It is probable that the outer hair cells effect the active mechanical amplification process responsible for delayed OAEs. This notion is supported by demonstrations of the motile features of outer hair cells.^{4,5} Moreover, the earlier observations that the cochlea's efferent system affects DPE amplitude^{6,7} indicate that the outer hair cells are also intimately involved in the DPE generation process, because the major outer hair cell innervation is efferent.⁸ Although delayed OAEs and DPEs have been shown to interact, the extent to which they originate from the same cochlear nonlinearity is not yet firmly established. Evidence that delayed OAEs are more sensitive to the effects of aspirin^{9,10} and that DPEs are present when hearing losses are severe enough to eliminate latent OAEs^{1,11} implies subtle differences in the generation of the two types of evoked emissions.

Because outer hair cells are uniquely sensitive to the cochlear injury that occurs during the early stages of many common hearing disorders, a number of investigators¹²⁻¹⁴ have argued for the potential utility of OAEs in a clinical setting in the form of "acoustic cochleography."¹³ Kemp et al¹³ were first to delimit the possible practical applications of OAE testing as a means to 1) screen objectively for

the normal mechanical status of the cochlea in neonates and young children, 2) establish a baseline of otoacoustic parameters of a patient for future use in detecting early changes in an ear, whether caused by heritable disease, drug treatment, or exposure to noise, 3) confirm the presence of a rare form of objective "physiologic" tinnitus representing cochlear "noise" that is easily masked, and 4) contribute toward a differential diagnosis of the cochlear nature of a particular hearing disorder.

Bray and Kemp,¹⁵ in fact, have been instrumental in developing TEOAEs in particular into a useful test for screening cochlear function in newborns and young children. Kemp et al¹³ have also tested the proficiency of this class of delayed evoked OAEs in detecting a number of common ear disorders. However, even though TEOAEs are sensitive to deficits in outer hair cell mechanical activity, it has not been possible as yet to establish useful differential diagnostic criteria with respect to different kinds of cochlear disorders based on measures of TEOAEs.

In contrast to TEOAEs, DPEs have a unique clinical potential because of their ability to be elicited at any chosen test frequency. This powerful aspect of DPE testing remains largely unexplored. To date, only a few reports have described human DPEs,^{10,13,16-19} and in most cases the frequency range examined was extremely limited. Moreover, the majority of the human studies have studied DPEs that originate from cochlear regions in which they were enhanced by nearby, strong evoked OAEs (TEOAEs, SFEs) or spontaneous otoacoustic emissions (SOEs).^{10,16,17} Consequently, the presumed ability to measure robust DPEs in all normally hearing humans at any test frequency remains to be established.

One of the principal interests of our laboratory is to investigate whether cochlear nonlinearity in the form of DPEs is useful as a clinical measure of cochlear function. Studies in experimental animals have shown the dependence of DPE amplitude on cochlear status in the region of the eliciting pure tones or primaries at f_1 and f_2 .²⁰⁻²² These basic findings support the notion that DPE testing has the potential to test the status of the micromechanical aspects of organ of Corti function in frequency-specific regions of the cochlea. The primary purpose of the present study was to collect parametric measures of DPEs in normally hearing subjects to provide a baseline against which otoacoustic activity in impaired ears could be compared. One of the two companion reports relates DPEs to a comprehensive analysis of the middle ear conduction system and to the generation of other emissions in the form of SOEs and SFEs (this Supplement, p 15). The other report describes a study of the clinical usefulness of DPEs determined by examining the influence of several cochlear disorders on the generation of acoustic distortion products (this Supplement, p 30).

EXPERIMENTAL PROTOCOL

Session 1	Session 2
Questionnaire	Otoscope examination
Otoscope examination	Tympanometry (226 Hz)
Standard audiogram (0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz)	Stimulus frequency emission (0.4-2 kHz)
Tympanometry (226, 630, 800, 1,000 Hz)	Spontaneous emissions (0.8-7.4 kHz)
Acoustic reflex (contralateral: 1, 2, 3, 4 kHz; ipsilateral: 1, 2 kHz)	Distortion product audiogram (1-8 kHz)
Spontaneous emissions (0.8-7.4 kHz)	Distortion product input-output series (1, 1.2, 1.5, 2, 2.3, 2.8, 3.5, 4.3, 5.3, 6.5, 8 kHz)

METHODS

SUBJECTS

Normative data were obtained from 44 ears of 22 healthy young adults (12 men and 10 women) with ages ranging from 21 to 30 years (mean, 24 years). The subjects, who were paid for their participation in the study, represented several ethnic groups (white, Asian, Hispanic, black) and demonstrated normal hearing sensitivity defined as pure-tone thresholds ≤ 10 dB hearing level (HL) (re: ANSI, 1969) for test frequencies at octave intervals from 0.25 to 8 kHz and at 3 and 6 kHz. Further, all subjects had normal middle ear function in terms of tympanometry patterns and acoustic reflex thresholds according to the findings of routine immittance testing. Finally, in response to direct questioning, subjects reported that they had no personal histories of long-term noise exposure, ototoxic drug administration, or ear infections, nor a family history that included known hereditary deafness.

Pure-tone audiometry and OAE testing were performed in a double-walled, electrically shielded sound isolation chamber (Industrial Acoustics Corp, 1205-A). During emissions testing, subjects were comfortably reclined in a lounge chair and were instructed to remain as quiet as possible.

Thirteen subjects (60%) demonstrated SOEs that were present in 21 of the 44 ears (48%). Eight (60%) of the 13 subjects exhibiting SOEs had emissions in both ears. All 44 ears exhibited SFEs. A detailed accounting of the acoustic characteristics of the SOEs and SFEs and the outcome of more detailed multifrequency-multicomponent immittance testing is provided in one of the companion reports (this Supplement, p 15).

GENERAL EXPERIMENTAL PROTOCOL

Pure-tone audiometry, aural immittance, and OAEs were tested during two experimental sessions that lasted about 2 hours each. Details of the testing protocol are outlined in the Table. During session 1, subjects completed a written questionnaire describing their general health and hearing histories. After the questionnaire had been reviewed with the subject, the condition of the external ear canals and

tympanic membranes was determined otoscopically, and if necessary, cerumen was removed by medical personnel. Standard pure-tone audiometry was performed, and detailed immittance testing at multiple frequencies was conducted. Finally, ears were examined bilaterally for the presence of SOEs. The second test session was conducted usually within a few days of the initial assessment period. During session 2, both ear canals and tympanic membranes were rechecked otoscopically, and tympanometry was again performed at the standard probe frequency of 226 Hz to ensure that middle ear function remained normal. The presence or absence of SOEs was redocumented, and measures of SFEs were performed. Finally, acoustic distortion product testing was conducted by acquiring DPE "audiograms" and a series of response-growth or input-output (I/O) functions. During both data collection sessions, brief rests were periodically provided between the individual tests.

AUDIOMETRIC TESTING

Pure tones at eight frequencies (0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz) were generated by a conventional screening audiometer (Belton 10-D) that had been calibrated according to accepted standards (ANSI, 1969). Thresholds were obtained in 5-dB steps by use of a routine clinical modified method of limits. Acoustic immittance measures, performed with a microcomputer-controlled (Apple, Macintosh Plus) tympanometer (Virtual, 310), included standard tympanometry that was performed with an 85-dB sound pressure level (SPL) tone at 226 Hz, and multifrequency tympanometry at one-third-octave intervals between 630 and 1,000 Hz. Immittance parameters included peak middle ear pressure, static admittance, estimated volume of the external ear canal, susceptance and conductance, pressure difference gradient, and phase angle. Acoustic reflexes were elicited with ipsilateral stimulation at 1 and 2 kHz and with contralateral stimulation at 1, 2, 3, and 4 kHz at levels ranging from 110 to 60 dB HL in 5-dB steps. Acoustic reflex thresholds, onset and offset latencies, and rise and fall times were calculated.

DISTORTION PRODUCT OTOACOUSTIC EMISSIONS TESTING

Stimuli. Two equilevel pure-tone signals, f_1 and f_2 ($f_1 < f_2$; $f_2/f_1 = 1.21$), were presented simultaneously at primary-tone frequencies that generated $2f_1 - f_2$ DPEs between 0.750 and 5.750 kHz. This range of frequencies was selected to represent medium- and upper-frequency regions that are routinely tested by conventional audiometric measures and the low-, medium-, and high-frequency limits that can be assessed currently by acoustic distortion products. The upper extent of the frequency range was determined largely by the limitations of the frequency response of the earphones. Basic work in humans and animals has established that the major

contribution to the emitted distortion product at $2f_1 - f_2$ is generated at a cochlear site near the f_2 place.^{22,23} An adequate representation of this place is provided by the geometric mean of the two primary-tone frequencies. Consequently, the DPE findings presented below are illustrated with respect to the geometric mean of the primary tones.

Acoustic distortion product "audiograms" were collected in 100-Hz steps at stimulus levels of 65, 75, and 85 dB SPL, with the geometric mean of f_1 and f_2 extending from 1 to 8 kHz. The expression DPE "audiogram" was selected to represent the frequency response of the DPE generation process because of the expectation that this response type would complement the frequency configuration of remaining hearing provided by the conventional audiogram. However, it should be noted that the DPE "audiogram" differs from the clinical audiogram in that the emitted form does not establish a true threshold response. Specific measures of the DPE "audiogram" included determinations of the frequencies of maxima and minima in decibels SPL and the general shape of the "audiogram" function. To better define the contour of the "audiogram," individual curves were smoothed by use of a conventional three-point running-average procedure. However, all statistical procedures were performed on unsmoothed data. In addition, I/O functions, generated by primary stimuli that were incremented in level in 5-dB steps from 25 to 85 dB SPL, were collected at 11 discrete frequencies located at quarter-octave intervals over the same frequency range as the "audiograms."

Generation and Measurement of $2f_1 - f_2$ DPEs. Stimuli were generated and DPEs were measured with essentially the same instrumentation described by Harris et al.¹⁹ Figure 1 illustrates a schematic of the stimulus generation and response-recording equipment along with an example of a spectrum of the ear canal signal showing a $2f_1 - f_2$ DPE. Briefly, both signal generation and response analysis were controlled by a laboratory microcomputer system (Digital Equipment Corp, 11/23). The two continuous primary tones at f_1 and f_2 were generated and attenuated separately by a two-channel frequency synthesizer (Hewlett Packard, 3326A) and associated programmable attenuators (Wavetek, 5P). The two signals were delivered independently to a pair of insert earphones (Etymotic Research, ER-2) that are characterized by a flat frequency response (0.2 to 10 kHz) and linear operation (up to 110 dB SPL) in the human ear canal. The primary tones were mixed acoustically and coupled via a short sound tube to a speculum that was sealed into the external ear canal with a foam eartip. The ear canal sound pressure was measured by a low-noise, sub-miniature microphone system (Etymotic Research, ER-10A), composed of four transducers that were incorporated into the speculum, and a low-noise

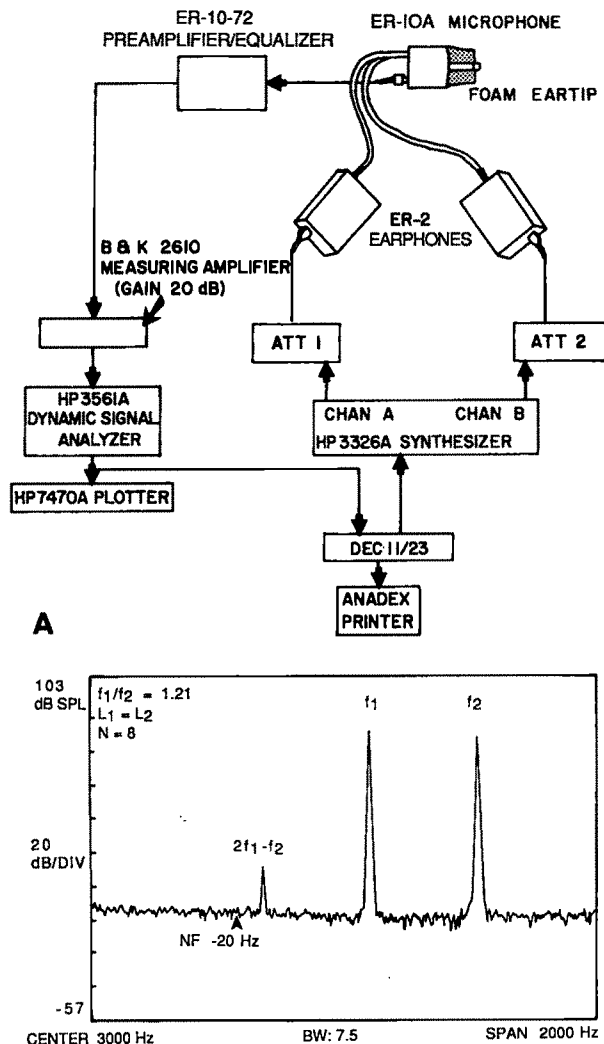
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Fig 1. Schematic representation of laboratory instrumentation used to collect distortion product emissions (DPEs). A) Microcomputer controls frequency synthesizer that generates two equilevel primary tones at f_1 and f_2 . Primaries are presented to ear canal via specially designed speculum containing miniature microphone system. Output of microphone is fed to dynamic signal analyzer to extract DPE at $2f_1 - f_2$ frequency. Stimulus frequencies and levels are automatically controlled, and elicited DPE amplitudes and corresponding noise floors are printed on-line and stored on disk. B) Actual spectrum of ear canal signal in human showing primary tones and DPE. Arrowhead — location 20 Hz below DPE at which noise floor of recording system was measured.

preamplifier-equalizer (Etymotic Research, ER-10-72).

A measuring amplifier (Bruel and Kjaer, 2620) provided an additional gain of +20 dB before the signal was delivered to a dynamic signal analyzer (Hewlett Packard, 3561A) for extraction of the Fourier components at the $2f_1 - f_2$ frequency. To provide a measure of the level of the noise floor, a Fourier analysis was also performed for the frequency 20 Hz below the DPE frequency. If the response at the $2f_1 - f_2$ frequency was at least 3 dB

above the level of the corresponding noise floor, a DPE was considered to be present. The span of the frequency window was set to 2 kHz, thus resulting in a 7.5-Hz analysis bandwidth that was shaped by a Hanning window weighting function. Eight spectral averages were performed to determine the final average of the amplitudes of the DPE and related noise floor. Quantitative DPE amplitude data were printed on-line and stored on disk for further off-line analysis. Instrumentation-related distortion measured on the signal analyzer was at least 80 dB below the primaries at the highest levels of stimulation. Related measurements in a 2-cm³ cavity representing the human ear canal indicated that in the presence of our standard bitonal stimulus regimen, distortion at the $2f_1 - f_2$ frequency was indistinguishable from the level of the associated noise.

The acoustic system and speculum-microphone assembly were calibrated according to the techniques used by Harris et al.¹⁹ Because the output of the speakers was designed to be essentially flat in the human ear canal from 0.2 to 10 kHz, a single 65-dB SPL pure tone (ie, at a constant voltage) was swept over this frequency range in 100-Hz steps in 10 ears of a separate group of five normally hearing subjects. The mean frequency response (± 1 SD) of the microphone system under these conditions indicated that over the majority of the frequency range of interest (ie, 1 to 10 kHz), the response of the system in the human ear canal was generally within 10 dB of the 65-dB signal. Following data collection, DPE levels at the various frequencies were adjusted for a particular ear according to the average 65-dB calibration function.

Data Collection. A complete DPE series on one ear, including both multilevel "audiograms" and multifrequency I/O functions that involved 296 separate measurements, was obtained before testing was begun on the second ear. A typical DPE test session required approximately 80 minutes, including the brief rest periods. At the beginning of the session, the system was calibrated for each ear by generating a 1-kHz tone at 65 dB SPL in one earphone of the probe assembly and monitoring the output from the microphone. If necessary, the probe was repositioned in the subject's ear canal and the attenuators were adjusted manually to achieve a 65-dB SPL output as indicated by the dynamic signal analyzer. In this manner, the influence of the physical attributes of each ear canal on the DPE measurements was minimized. Both the probe and the attenuators remained unchanged following these adjustments.

RESULTS

Audiometric testing showed that all subjects had hearing levels of 10 dB or better. In addition, the standard middle ear function testing indicated that

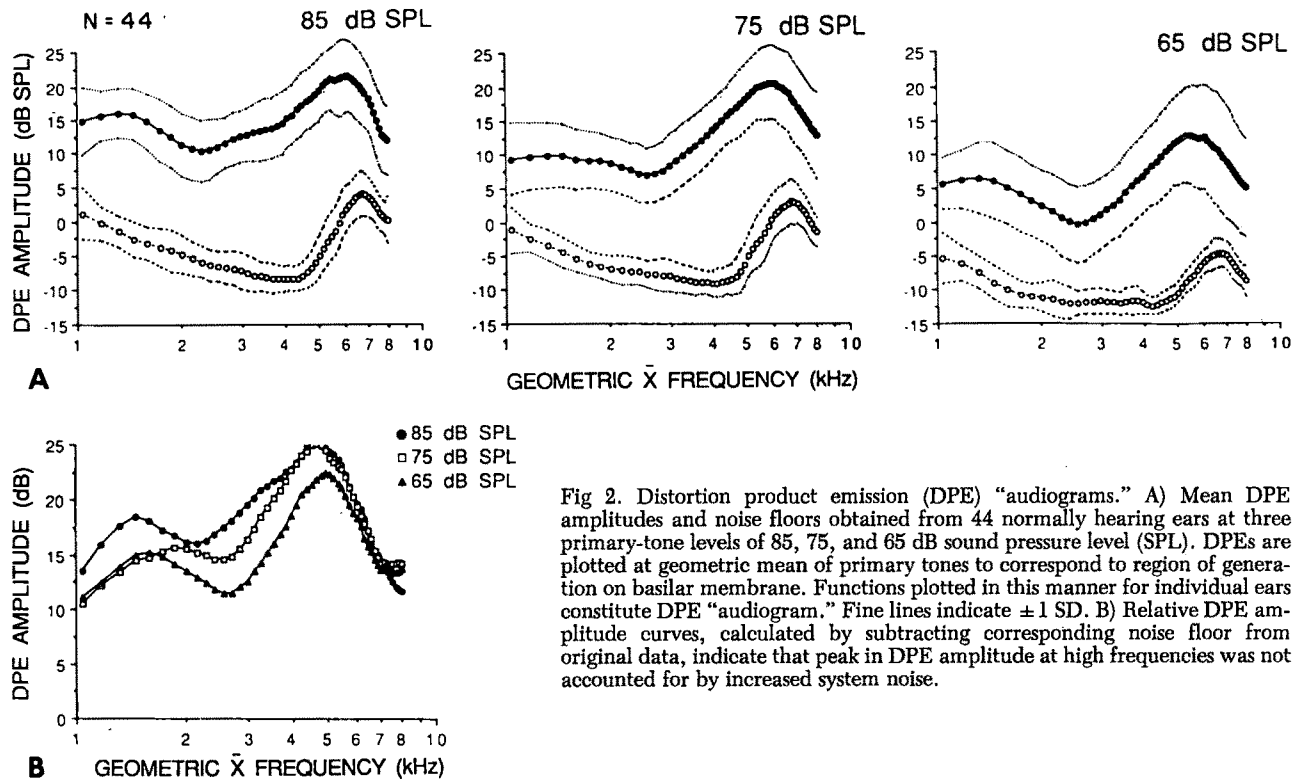


Fig 2. Distortion product emission (DPE) "audiograms." A) Mean DPE amplitudes and noise floors obtained from 44 normally hearing ears at three primary-tone levels of 85, 75, and 65 dB sound pressure level (SPL). DPEs are plotted at geometric mean of primary tones to correspond to region of generation on basilar membrane. Functions plotted in this manner for individual ears constitute DPE "audiogram." Fine lines indicate ± 1 SD. B) Relative DPE amplitude curves, calculated by subtracting corresponding noise floor from original data, indicate that peak in DPE amplitude at high frequencies was not accounted for by increased system noise.

immittance values were within normal limits for all ears. Thus, in response to 226-Hz probe tones, tympanograms for every ear represented the simple, bell-shaped type A pattern,^{24,25} with one admittance peak occurring between -19 and $+38$ decapascals. In addition, in response to 1-kHz tonebursts, both contralateral and ipsilateral reflexes were evoked in every ear. Further, thresholds for contralateral reflexes were <95 dB HL, whereas those for ipsilateral reflexes were within 10 dB of corresponding contralateral thresholds, ie, ≤ 90 dB HL. More complete details of the results of the specialized middle ear tests at other test frequencies are presented in the subsequent report (this Supplement, p 15).

Analysis of DPEs from the 44 ears showed that all ears had measurable DPEs that were considerably above the noise floor of the recording system. The average emission amplitude from these ears compared to the noise floor is presented in the form of the DPE "audiogram" functions of Fig 2A for the three primary-tone levels. It is evident from these curves that DPE amplitude peaked in two frequency ranges, with one maximum around 1.5 kHz and another peak at approximately 5.5 kHz. A conspicuous dip in the amplitude function occurred between these two maxima at about 2 to 3 kHz for all levels of stimulation. In the low-frequency region, DPE amplitude reached a maximum of 17 dB SPL, whereas at high frequencies, DPEs attained a level of approximately 23 dB SPL.

Depending upon the frequency and level of the

primary tones, DPE amplitudes ranged from around 50 to 70 dB below the level of the primaries. In the high frequencies, the noise floor of the recording system also demonstrated a peak that was approximately coincident with the high-frequency maximum in DPE amplitude. However, subtraction of the noise floor values from the corresponding DPE amplitudes resulted in the curves displayed in Fig 2B, in which the overall contours remained relatively unchanged. These results indicate that DPE levels actually increased at high frequencies and were not elevated artifactually by the increased noise introduced by the stimulus-generating equipment at higher frequencies. The plots of Fig 2B, showing the relative amplitudes of the three DPE "audiogram" functions, also illustrate the lack of linearity in both the low- and high-frequency maxima in response to increased primary-tone levels. It is clear from the plots of Fig 2A, however, that the variability shown by the dashed lines representing ± 1 SD remained relatively constant across frequency.

Average I/O functions collected at the 11 individual test frequencies are depicted in Fig 3. These curves indicate that DPE responses in humans have dynamic ranges of approximately 40 dB. Further, the mean maximum amplitudes gradually increased as primary frequencies increased, until about 5.3 kHz, where the largest DPEs were about 30 dB above the noise floor. Moreover, detection "thresholds" were reasonably constant across frequency in that they varied between 40 and 45 dB SPL in response to low- and high-frequency primaries and

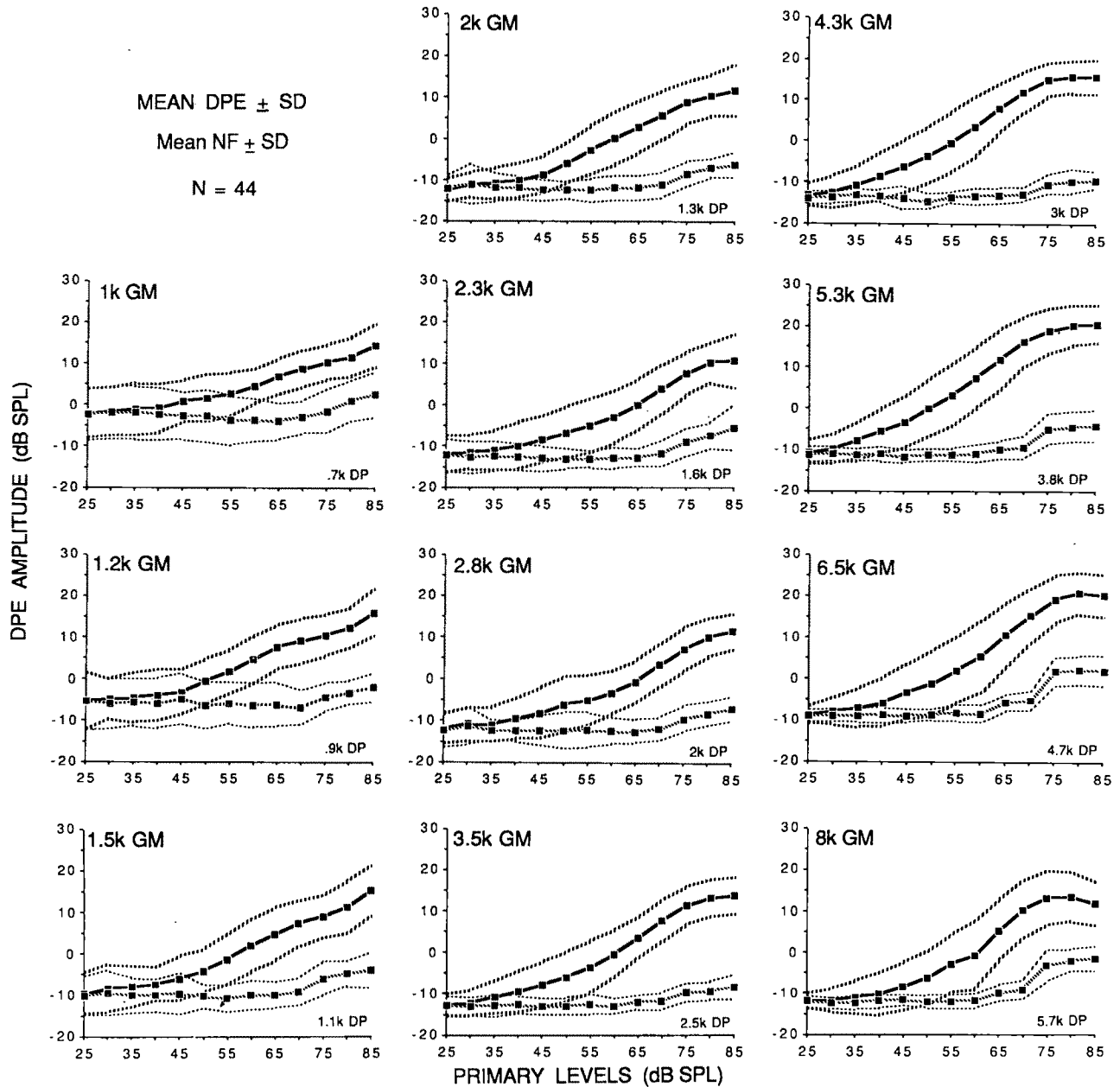


Fig 3. Distortion product emission (DPE) input-output functions and associated noise floors (NF) obtained at 11 quarter-octave intervals throughout frequency range used for DPE "audiogram" measurements. Note that dynamic ranges and slopes for these functions depend upon frequency region tested. Fine lines indicate ± 1 SD.

remained between 35 and 40 dB SPL for middle-frequency tones.

Detailed examination of the individual curves of Fig 3 reveals that at lower frequencies, the functions were very linear, whereas around 3.5 kHz and higher, they exhibited saturation in response to stimulus levels greater than about 75 dB SPL. These functions also showed relatively constant variability, indicated by the dashed lines (± 1 SD) across both frequency and level. The slopes of the I/O functions calculated over the 55- to 65-dB SPL stimulus range are plotted for the 11 frequencies in Fig 4. It is clear from inspection of this curve that the growth of the I/O functions became steeper as DPE

frequency increased. However, although the growth of distortion was greater at higher frequencies, the gain of the function at $2f_1 - f_2$ was typically less than 1.

Several measures were calculated from the I/O functions for each ear at representative frequencies distributed throughout the DPE test range that were closest to 1, 2, 4, 6, and 8 kHz. These measures included the DPE amplitude elicited at the 75-dB SPL primary-tone levels and the detection "threshold" of the emitted response in terms of the primary-tone levels required to produce a response that was 3 dB above the noise floor. These particular metrics contributed toward determining wheth-

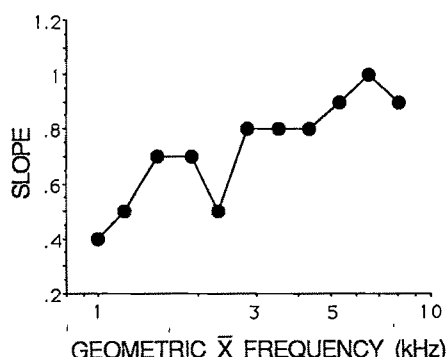


Fig 4. Plot of slopes on input-output curves as function of test frequency. Slopes were calculated from linear region of dynamic range functions between primary-tone levels of 55 and 65 dB sound pressure level. Clear tendency for distortion product emissions to grow faster as stimulus level is increased can be observed for higher-frequency primary tones.

er DPEs from right and left ears were correlated and whether DPE amplitude was related to "threshold."

Figure 5 depicts scatterplots relating DPE amplitudes and "thresholds" from the right and left ears of each subject at the five representative test frequencies. It is evident from the configuration of the data points in Fig 5A that there was a reasonably strong relationship between the emission amplitudes from both ears of the same individual, especially at the higher frequencies. Conventional correlational analyses (ie, the Pearson product-moment correlation coefficient) supported this impression: 1 kHz: $r = .42$, $p > .05$; 2 kHz: $r = .38$, $p > .05$; 4 kHz: $r = .65$, $p < .001$; 6 kHz: $r = .60$, $p < .005$; 8 kHz: $r = .82$, $p < .001$. Acoustic distortion product "thresholds" were also correlated between a particular subject's ears, but to a lesser degree than amplitude (1 kHz: $r = .54$, $p < .01$; 2 kHz: $r = .42$, $p > .05$; 4 kHz: $r = .49$, $p < .05$; 6 kHz: $r = .38$, $p > .05$; 8 kHz: $r = .61$, $p < .005$). The scarcity of data points in the upper left and lower right quadrants of Fig 5A attests to the similarity of DPE amplitudes between ears. However, the spread of data points into these regions in Fig 5B indicates that DPE "thresholds" were sometimes different by more than 20 dB between ears.

Because DPE amplitudes and "thresholds" were related between ears, mean values for these measures were computed for the left and right ears of each subject. In this manner, the relationship between "threshold" and DPE magnitude (right and left ears averaged) in response to suprathreshold stimuli could be examined. Figure 6 displays a scatterplot showing the mean DPE amplitude at the five representative test frequencies with respect to the mean detection "threshold" level for all 22 subjects. It is evident from this plot that on the whole there was a tendency for subjects with large DPEs to have low "thresholds" (1 kHz: $r = .39$, $p > .05$; 2 kHz: $r = .51$, $p < .05$; 4 kHz: $r = .47$, $p < .05$; 6 kHz:

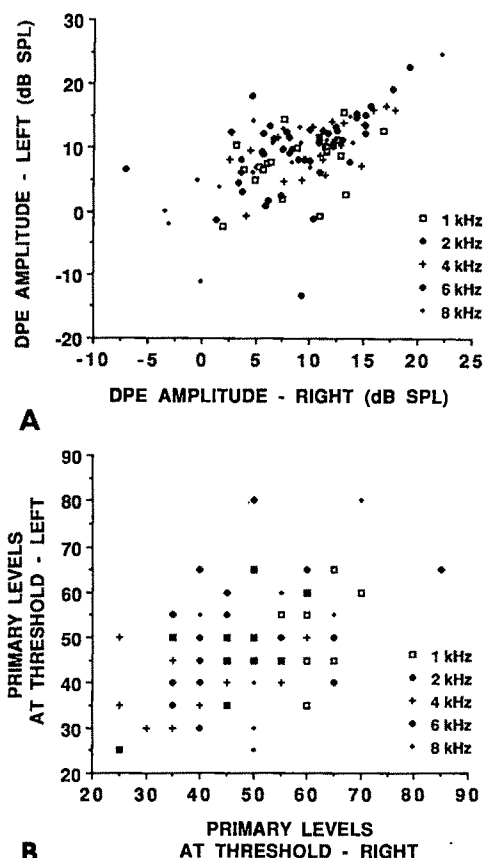


Fig 5. Scatterplots showing relationship between distortion product emission (DPE) measures from right and left ears of same individual. A) Relation of DPE amplitude evoked by 75-dB sound pressure level (SPL) primaries from right and left ears of all subjects for five test frequencies. It can be seen that DPE amplitudes from different ears of same subject tended to be related regardless of test frequency. B) Comparison of DPE detection thresholds from right and left ears. As with DPE amplitudes, DPE "thresholds" from different ears of same subject tended to be correlated.

$r = .88$, $p < .001$; 8 kHz: $r = .78$, $p < .001$). Thus, it follows that the individuals with the largest DPEs tended to have the greatest dynamic ranges.

A comparison of DPE amplitudes and "thresholds" from male versus female ears failed to reveal any significant differences except at 4 kHz. A statistical comparison (Student's t test) of 4-kHz DPEs from men and women revealed that on average, women demonstrated significantly ($p < .01$) lower "thresholds" by about 10 dB. It is interesting to note that the lower DPE "thresholds" at 4 kHz for women occurred in the absence of differences in hearing thresholds between the two genders. In addition, a tendency for women to exhibit slightly larger DPEs in response to 75-dB SPL primaries was also observed for 4-kHz emissions, but this tendency was not statistically significant.

Close inspection of the DPE "audiograms" from each of the 44 ears revealed that several patterns specific to the individual ears could be distinguished that differed substantially from the mean DPE

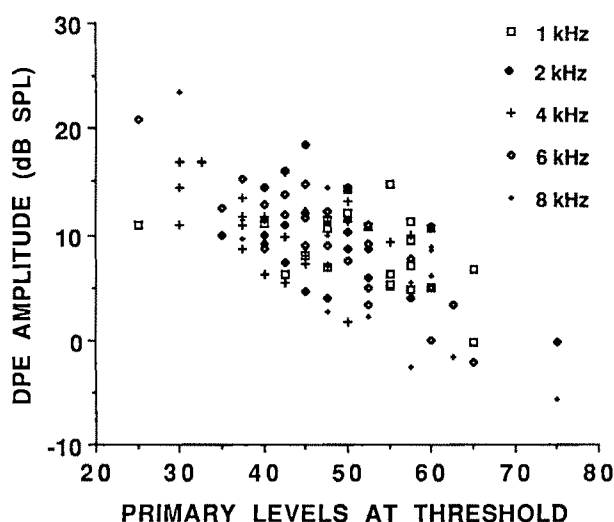


Fig 6. Scatterplot of data averaged across right and left ears depicting relation between distortion product emission (DPE) amplitude produced by 75-dB sound pressure level (SPL) primary tones and level of primary tones required to evoke "threshold" DPE response. It is evident that at all five frequencies examined there was strong tendency for subjects with large-amplitude DPEs to have lower "thresholds."

functions. Such identifiable patterns included ears with very low response levels in the 1- to 1.5-kHz range ($n = 3$), ears with significant amplitude decrements in response to middle-frequency primaries between about 2 and 5 kHz ($n = 5$), and a final group of ears with substantially lower-amplitude DPEs in the high-frequency range extending from 5 to 8 kHz ($n = 5$). The averages of these various sub-classifications in response to 75-dB SPL primaries are compared to the corresponding mean population function in Fig 7. The differences between the subgroup contours and the overall curve are obvious for the low- and high-frequency loss groups. However, this distinction is less evident for the group of ears demonstrating middle-frequency decrements. The lack of an obvious difference between the trajectories of the mean and middle-frequency loss curves was likely due to the observation that the distinctive middle-frequency dips in DPE amplitude occurred at dissimilar frequencies that were unique to the individual function that determined the subgroup curve. Thus, once the five DPE "audiograms" were averaged together, the dips tended to disappear. An example of a typical middle-frequency loss pattern for one ear is provided in Fig 8 of the following paper (this Supplement, p 26).

The irregular patterns shown in Fig 7 exclude one individual with extremely large DPEs in both ears that extended over a frequency range that corresponded approximately to the deficit region in the ears exhibiting high-frequency decrements in DPE amplitudes. Surprisingly, average curves calculated on a data base that selectively eliminated the 15 DPE "audiograms" showing the irregular patterns, ie, the mean curve for the 29 remaining ears, did

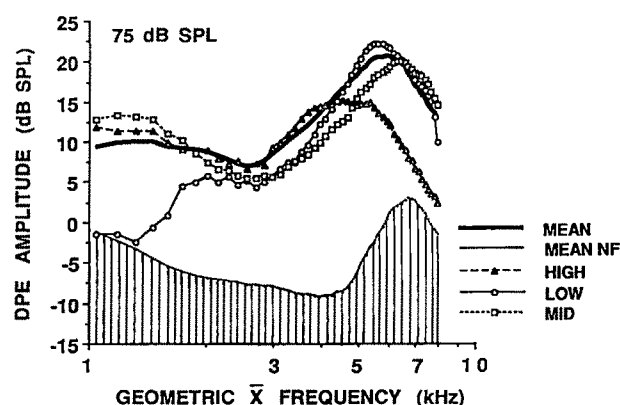


Fig 7. Mean distortion product emission (DPE) "audiograms" for all 44 ears (heavy solid line) in response to 75-dB sound pressure level (SPL) primaries, compared to average "audiograms" from three subpopulations of "irregular" ears that differed from overall pattern of response. Irregular ears comprised group with low DPE amplitudes in response to high-frequency primaries (triangles), group with reduced low-frequency amplitudes (circles), and group with prominent amplitude dips in middle frequencies (squares). Contour of last group's response appeared very similar to overall curve, because dips occurred at different frequencies for separate individuals and thus tended to cancel when averaged. Vertical striping and dotted line — average noise floor (NF) of recording system.

not differ substantially from the mean amplitude and variability functions displayed in Fig 2A for all 44 ears.

Because the normally hearing subjects ranged in age from 21 to 30 years, it seemed reasonable to assume that age may have accounted for the differences observed between the regular and irregular DPE patterns. However, the mean age (23.4 years) of the persons with irregular patterns was virtually identical to the age of those subjects in which both ears conformed to the overall average pattern. It should be noted, however, that four of the five ears exhibiting the high-frequency loss pattern came from the two oldest subjects, a 30-year-old man and a 30-year-old woman. Consequently, the mean DPE amplitudes and "thresholds" (right and left ears averaged) at the five standard test frequencies were statistically related to the ages of the 22 subjects. The results of these comparisons revealed significant age-related correlations for the two highest test frequencies at 6 kHz (amplitude: $r = .45$, $p < .05$; "threshold": $r = .58$, $p < .005$) and 8 kHz (amplitude: $r = .50$, $p < .05$; "threshold": $r = .46$; $p < .05$). Scatterplots of the relationships between DPE amplitude or detection "threshold" and subject age are shown for 6 and 8 kHz in Fig 8A and Fig 8B, respectively. These plots show a mild but significant effect of age on the DPE responses obtained from our subjects. Because all subjects demonstrated normal hearing levels and middle ear function at standard test frequencies, the significant relationship between age and the emission parameters of "threshold" and amplitude suggests that the higher-frequency DPEs may be sensitive to the early effects

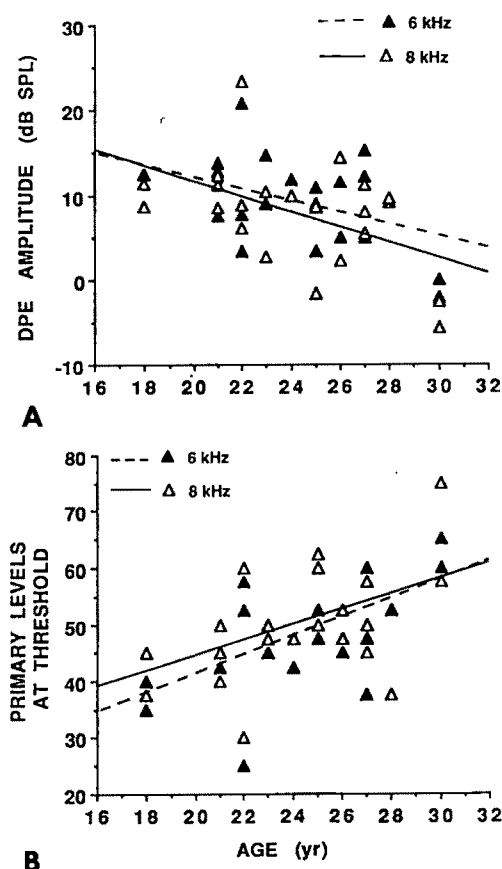


Fig 8. Scatterplots relating subject ages to mean distortion product emission (DPE) measures from right and left ears. Straight lines — regression lines fitted to data. A) DPE amplitude correlated with subject age at 6 and 8 kHz in that, at both frequencies, significant negative correlation was obtained between DPE amplitude and age of individual. B) DPE detection thresholds plotted against subject age, showing significant positive correlations between "threshold" and age.

of aging, prior to a detectable influence from presbycusis on hearing as tested by standard clinical audiometry.

DISCUSSION

Distortion products in the form of audible cubic difference tones have been studied extensively in normally hearing persons by use of psychophysical techniques. However, relatively little systematic information exists concerning the principal characteristics of acoustic distortion in humans. In an early study, Kemp and Brown¹⁸ demonstrated in several subjects that many DPE characteristics in humans, including tuning properties, are comparable to those measured in experimental animals. Additionally, in a detailed study of the effects of the f_2/f_1 ratio on human DPE amplitudes, Harris et al¹⁹ confirmed the impressions of several earlier reports^{16,17} suggesting that the most effective f_2/f_1 ratio was around 1.2. Recently, Kemp et al¹³ measured DPEs in 14 normal ears, thus providing the most detailed description to date of these responses in humans. These workers illustrated, in a few additional sub-

jects, several instances in which the frequency pattern of decrements in DPE amplitudes closely mimicked the extent of clinically measured hearing losses.

The primary purpose of the present study was to collect systematic information describing DPEs in normally hearing humans by performing a detailed parametric study of the $2f_1 - f_2$ distortion product. These baseline measures are essential in developing a data base against which the results of detailed studies of DPEs in clinical populations manifesting various hearing disorders could be compared. Distortion product emissions were investigated comprehensively by two basic approaches. The first technique, in the form of DPE "audiograms," enabled the emission amplitudes at closely spaced intervals in the stimulus frequency domain to be examined. In a complementary manner, the second procedure permitted the relationship between response amplitude and stimulus level to be investigated by use of fine gradations in the stimulus magnitude domain. Both types of analyses showed that on average, normally hearing ears generate a considerable amount of biomechanical activity as measured by acoustic distortion products.

In examining the averaged DPE data, we noted a number of salient features. For example, the contour of the DPE "audiogram" describing emission magnitude with respect to systematic variations in primary-tone frequencies suggested that the maximum response energy was generated in two specific frequency regions, regardless of the levels of the primaries. One peak energy region was associated with lower-frequency primaries around 1.5 kHz, and the other region of maximum response was related to higher-frequency primaries at approximately 5.5 kHz. Between these two energy peaks was a middle-frequency region consisting of smaller-amplitude DPEs. It is noteworthy that this dip was displaced toward lower frequencies as the levels of the primaries increased. These findings, as well as the effects of stimulus level on the peak region of the DPE f_2/f_1 ratio function,¹⁹ are in accordance with observations of similar shifts in peak basilar membrane displacements with increased stimulus levels.²⁶ Such similarities between the two types of findings suggest that basilar membrane mechanics are responsible for DPE primary-tone-level phenomena.

Virtually every one of the 44 ears tested displayed a dip or at least a plateau in the middle-frequency region of the DPE "audiogram" function. Although the dip frequency was similar between the two ears of the same individual, it varied between 2 and 4 kHz across the ears of different subjects. The precise nature of the middle-frequency decline in DPE amplitude exhibited by normally hearing ears is unknown at this time. Probably, it was caused by an interaction of the resonances common to a particular individual's middle ear and cochlea. The lower-

frequency peak of the DPE "audiogram" is consistent with the frequency region associated with optimal middle ear conduction of acoustic signals. Moreover, the majority of SOEs and the maximum energy peak in TEOAEs are concentrated within the same frequency region.¹³ In contrast, the DPE maximum at the higher frequencies was unexpected, because middle ear transmission attenuates OAEs in this frequency range. The sizable DPEs at high frequencies imply that within the cochlea these distortion products are very large indeed. This suggestion is also consistent with the steeper slopes and saturating responses of I/O functions elicited by high-frequency primaries. Together, both the "audiogram" and I/O data support the existence of a different rate of DPE growth in response to increased stimulus levels at high frequencies.

The average human DPE I/O functions displayed monotonic shapes with slopes <0.8 in response to primaries described by geometric means between 1 and 2 kHz. For frequencies higher than 2 kHz, the I/O functions demonstrated steeper slopes that approached unity, along with a tendency to saturate at the highest stimulation levels. Although the variability between ears was appreciable, as evidenced by the extent of the ± 1 -SD areas, a considerable portion of each function was well above noise floor levels. Several uniform DPE properties exhibited by I/O functions from the normally hearing population included a dynamic range of about 35 to 40 dB that was fairly constant across frequencies, and detection "thresholds" that were generally within 10 dB of each other.

Overall, the "audiogram" and I/O function data agreed quite well with the preliminary data reported by Kemp et al¹³ for 14 normally hearing ears. Thus, the DPEs of the present study were measurable over a similar frequency range with roughly the same variability. However, the dynamic range of the present findings was slightly larger, with DPEs having higher amplitudes accompanied by a higher system-noise floor. These small discrepancies probably are attributable to the different instrumentation and calibration procedures used in the two studies.

Although the majority of ears (29/44) were capable of generating reasonably substantial DPEs at all test frequencies, about one third (15/44) of the ears demonstrated significant deficiencies in the production of emissions within restricted frequency regions. It is tempting to attribute the high-frequency deficits observed for five ears as being due largely to aging effects, because four of these instances were observed in both ears of the two oldest (30 years) individuals tested. Ascribing the cause of the high-frequency deficit in the remaining ear, from a 22-year-old subject, to presbycusis is more problematic, because it is unlikely that the aging factor is either unilaterally distributed or expressed

in such a young ear.

Attributing a specific cause to the prominent low- and middle-frequency decrements in DPE activity that were observed for eight other ears is more difficult. That six of these ears were from three subjects supports the notion that the irregularities were probably due to factors that influenced both cochleas similarly, ie, excessive noise exposure or genetically determined influences. Other possible contributing factors, including discrete deficits in middle ear transmission or the influence of other emission types, are discussed in a companion report (this Supplement, p 15). Finally, there appears to be no obvious explanation for the markedly enhanced high-frequency DPEs noted for the two ears of a single subject. It is noteworthy that in rabbit models of both sound-induced cochlear damage²⁷ and endolymphatic hydrops,²⁸ experimental animals occasionally demonstrate similar hyperactivity in high-frequency regions before permanent reductions in DPE activity occur. It may be informative to retest this particular individual's ears at a later date to assess whether a pathologic response eventually developed.

In the presence of normal hearing, DPE amplitudes and "thresholds," especially those associated with high-frequency primary tones, were significantly correlated with the subject's age. Such a relationship suggests that DPEs may detect discrete pathologic alterations in the cochlea prior to their detection by clinical audiometric tests. The sensitivity of DPEs to subclinical changes is also supported by the observed differences in "thresholds" at 4 kHz between men and women. Presumably, men are exposed more than women to loud sounds over a lifetime. Kemp et al¹³ observed that TEOAEs were not always present at 4 kHz, but these investigators did not relate this observation to subject gender. The fine sensitivity of DPEs and TEOAEs to cochlear status suggests the possibility that standardizing emission test procedures may be exceedingly difficult, in that these responses seem to be sensitive to many variables that are not readily detectable by traditional audiometric procedures.

In the 10 years since the discovery of OAEs, a number of investigators have proposed that emitted responses may form the basis of a clinical test of cochlear dysfunction.¹²⁻¹⁴ However, there have been few attempts to test this notion systematically. To date, the TEOAEs have been the only class of OAE that has been investigated methodically for this purpose. These emissions can also be detected in the ears of essentially all normally hearing humans.^{12-14,29} However, because TEOAEs are closely linked to the structural properties of the organ of Corti in specific frequency regions, their numbers, frequency content, and tuning characteristics vary widely among subjects in a manner similar to that noted for SOEs. These findings are typical of the

mechanistic class of emissions that Kemp² termed "place-fixed" or long-latency emissions, which include SOEs, SFEs, and TEOAEs. In the case of place-fixed emissions, the large variability in magnitude and frequency extent observed across ears makes them unsuitable for deliberate tests of definitive cochlear sites.

In contrast, DPEs belong to the class of emitted response that Kemp² defined as "wave-fixed" emissions. Rather than being closely associated with structural aspects of the organ of Corti, DPEs are related more directly to energy that escapes from the nonlinear interactions of two frequency-specific traveling waves between their respective generation sites on the cochlear partition. Thus, DPEs can be used to purposively examine any specific frequency region of the cochlea.

The principal motivation for performing the present study was to investigate the properties of DPEs in normally hearing subjects in order to determine if uniform features could be identified that would be useful in distinguishing pathologic from normal ears. According to our measures of DPEs, both right and left ears of a particular subject are equally capable of generating a considerable amount of biomechanical activity across a rather extensive frequency range. Additionally, in contrast to observations that have been made in the study of SOEs,³⁰ an increased prevalence of DPEs in female compared to male ears was not observed. Thus,

DPEs appear to represent a general cochlear phenomenon that does not display the idiosyncrasies that may make the other emission types less clinically useful.

However, within our range of test frequencies, individual patterns of responsiveness were identified for which the responsible source remains to be determined. Moreover, in general, response variability was great enough that traditional clinical definitions of abnormality, based on patient values greater than ± 2 SD, cannot be applied appropriately to DPEs at this time. If an explanation for the amplitude dips observed in some "normal" ears is found, then a departure from the overall normal DPE pattern, rather than absolute amplitudes or "thresholds," may be the most clinically relevant feature of these emissions. However, the significant correlation between DPE detection "threshold" and amplitude in response to 75-dB SPL primaries supports the likelihood that a test based upon a single stimulus level can be developed. For example, a short test that assesses DPEs at about 50 discrete frequencies in response to 75-dB SPL primaries would be compatible with the reasonably brief examination periods that are available in clinical settings. Thus, as an objective, noninvasive test of the normal biomechanical activity of the cochlea, DPEs from normal ears can be characterized as having a set of relatively uniform properties against which the status of an unknown ear can be determined.

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REFERENCES

1. Kemp DT. Stimulated acoustic emissions from within the human auditory system. *J Acoust Soc Am* 1978;64:1386-91.
2. Kemp DT. Otoacoustic emissions, travelling waves and cochlear mechanics. *Hear Res* 1986;22:95-104.
3. Zwicker E. Delayed evoked oto-acoustic emissions and their suppression by gaussian-shaped pressure impulses. *Hear Res* 1983;11:359-71.
4. Brownell WE, Bader CR, Bertrand D, de Ribaupierre Y. Evoked mechanical responses of isolated cochlear outer hair cells. *Science* 1985;227:194-6.
5. Zenner HP, Zimmermann U, Schmitt U. Reversible contraction of isolated mammalian cochlear hair cells. *Hear Res* 1985;18:127-33.
6. Mountain D. Changes in endolymphatic potential and crossed olivocochlear bundle stimulation alter cochlear mechanics. *Science* 1980;210:71-2.
7. Siegel JH, Kim DO. Efferent neural control of cochlear mechanics? Olivocochlear bundle stimulation affects cochlear biomechanical nonlinearity. *Hear Res* 1982;6:171-82.
8. Spoendlin H. Innervation densities of the cochlea. *Acta Otolaryngol (Stockh)* 1972;73:235-48.
9. Martin GK, Lonsbury-Martin BL, Probst R, Coats AC. Spontaneous otoacoustic emissions in a nonhuman primate. I. Basic features and relations to other emissions. *Hear Res* 1988;33:49-68.
10. Wier CC, Pasanen EG, McFadden D. Partial dissociation of spontaneous otoacoustic emissions and distortion products during aspirin use in humans. *J Acoust Soc Am* 1988;84:230-7.
11. Martin GK, Whitehead ML, Lonsbury-Martin BL. Potential of evoked otoacoustic emissions for infant hearing screening. *Semin Hear* 1990;11:186-204.
12. Elberling C, Parbo J, Johnsen NJ, Bagi P. Evoked acoustic emission: clinical application. *Acta Otolaryngol [Suppl] (Stockh)* 1985(suppl 421):77-85.
13. Kemp DT, Bray P, Alexander L, Brown AM. Acoustic emission cochleography — practical aspects. *Scand Audiol [Suppl]* 1986(suppl 15):71-96.
14. Probst R, Coats AC, Martin GK, Lonsbury-Martin BL. Spontaneous, click-, and toneburst-evoked otoacoustic emissions from normal ears. *Hear Res* 1986;21:261-75.
15. Bray P, Kemp DT. An advanced cochlear echo technique suitable for infant screening. *Br J Audiol* 1987;21:191-204.
16. Kemp DT. Evidence of mechanical nonlinearity and frequency selective wave amplification in the cochlea. *Arch Otorhinolaryngol* 1979;224:37-45.
17. Wilson JP. The combination tone, 2f₁ - f₂, in psychophysics and ear-canal recording. In: van den Brink G, Bilsen FA, eds. *Psychophysical, physiological, and behavioral studies in hearing*. Delft, the Netherlands: Delft University Press. 1980:43-52.
18. Kemp DT, Brown AM. A comparison of mechanical nonlinearities in cochleae of man and gerbil from ear canal measurements. In: Klinke R, Hartmann R, eds. *Hearing — physiological bases and psychophysics*. New York, NY: Springer Verlag, 1983:82-8.
19. Harris FP, Lonsbury-Martin BL, Stagner BB, Coats AC, Martin GK. Acoustic distortion products in humans: systematic

changes in amplitude as a function of f_2/f_1 ratio. *J Acoust Soc Am* 1989;85:220-9.

20. Kim DO, Molnar CE, Matthews JW. Cochlear mechanics: nonlinear behavior in two-tone responses as reflected in cochlear-nerve-fiber responses and in ear-canal sound pressure. *J Acoust Soc Am* 1980;67:1704-21.

21. Clark WW, Kim DO, Zurek PM, Bohne BA. Spontaneous otoacoustic emissions in chinchilla ear canals: correlation with histopathology and suppression by external tones. *J Acoust Soc Am* 1984;71:405-9.

22. Martin GK, Probst R, Coats AC, Lonsbury-Martin BL. Acoustic distortion products in rabbits. II. Sites of origin revealed by suppression and pure-tone exposures. *Hear Res* 1987;28:191-208.

23. Brown AM, Kemp DT. Suppressibility of the $2f_1 - f_2$ stimulated acoustic emissions in gerbil and man. *Hear Res* 1984;13:29-37.

24. Jerger JF. Clinical experience with impedance audiometry. *Arch Otolaryngol* 1970;92:311-24.

25. Liden G, Harford E, Hallen O. Tympanometry for the diagnosis of ossicular disruption. *Arch Otolaryngol* 1974;99:23-9.

26. Rhode WS. Observations of the vibration of the basilar membrane in squirrel monkeys using the Mossbauer technique. *J Acoust Soc Am* 1971;49:1218-31.

27. Franklin DJ, Stagner BB, Lonsbury-Martin BL, Martin GK. Altered susceptibility of the inner ear following repeated noise exposure. *J Acoust Soc Am* 1988;83:S115.

28. Martin GK, Stagner BB, Coats AC, Lonsbury-Martin BL. Endolymphatic hydrops in rabbits: behavioral thresholds, acoustic distortion products, and cochlear pathology. In: Nadol JB Jr, ed. *Second International Symposium on Meniere's Disease*. Boston, Mass: Harvard University Press, 1989:205-19.

29. Bonfils P, Uziel A, Pujol R. Evoked oto-acoustic emissions from adults and infants: clinical applications. *Acta Otolaryngol (Stockh)* 1988;105:445-9.

30. Strickland E, Burns EM, Tubis A. Incidence of spontaneous otoacoustic emissions in children and infants. *J Acoust Soc Am* 1985;78:931-5.

DISTORTION PRODUCT EMISSIONS IN HUMANS II. RELATIONS TO ACOUSTIC IMMITTANCE AND STIMULUS FREQUENCY AND SPONTANEOUS OTOACOUSTIC EMISSIONS IN NORMALLY HEARING SUBJECTS

BRENDA L. LONSBURY-MARTIN, PhD

FRANCES P. HARRIS, PhD

MARGARET D. HAWKINS

BARDEN B. STAGNER

GLEN K. MARTIN, PhD

HOUSTON, TEXAS

Multifrequency and multicomponent evaluations of aural acoustic immittance, including tympanometry and acoustic reflex testing, were performed on 44 normal ears to examine the influence of middle ear functioning on the generation and detection of distortion product otoacoustic emissions (DPEs). In the same ears, the prevalence and parametric features of spontaneous and stimulus frequency emissions were also assessed so that their relationship to the detection "thresholds" and amplitudes of corresponding DPEs could be determined. The general outcome was that none of the examined features of acoustic immittance provided an explanation for the discrete, low-amplitude DPE regions observed in about one third of normal ears. Moreover, the presence of typical spontaneous and stimulus frequency emissions in these same "irregular" ears indicated that emission generation and reverse cochlear transmission were also operating normally within these regions of reduced DPEs. Consequently, other, as yet undetermined influences appear to contribute to the DPE variability noted in some ears. Finally, the simultaneous presence of stimulus frequency emissions, but not spontaneous emissions, appeared to reduce the detection "thresholds" and increase the amplitudes of low-frequency DPEs.

KEY WORDS — acoustic reflex, human distortion product emissions, spontaneous emissions, stimulus frequency emissions, tympanometry.

INTRODUCTION

Distortion product otoacoustic emissions (DPEs) can be recorded in essentially all normally hearing individuals^{1,2} (see also this Supplement, p 3). However, recent work has indicated that although the majority of a sample of normal ears generated DPEs throughout an extensive frequency range (ie, from 1 to 8 kHz), approximately one third of the ears exhibited DPEs with significantly reduced amplitudes within restricted frequency regions (this Supplement, p 3). In addition, another two ears from one individual exhibited high-frequency DPEs that were considerably larger than average. Ears demonstrating an "irregular" emission pattern consisting of reduced DPE amplitudes could be divided into three subgroups based upon the frequency extent over which atypical DPEs were measured. Thus, these ears were classified as demonstrating a low- (1 to 1.5 kHz), middle- (2 to 4 kHz), or high-frequency (5 to 8 kHz) DPE loss pattern.

Several possibilities might account for an ear's inability to generate robust DPEs. Potential explanations of "irregular" DPEs include 1) stimulus variables relating to, for example, the association of the frequencies (f_1, f_2) or levels (L_1, L_2) of the two primary tones, ie, the f_2/f_1 ratio or the $L_1 - L_2$ difference, respectively, that were not optimal at certain sites within these cochleas and therefore contributed to the inconsistent generation of DPEs; 2) frequency-specific anomalies in the forward and/or reverse middle ear transmission of the acoustic signal that reduced DPE amplitudes selectively; or

3) subclinical pathologic changes that caused deficits in cochlear or middle ear function and went undetected by conventional audiometric tests. The present study was designed to investigate the latter two possibilities by relating DPE amplitudes and "thresholds" to the multifrequency and multicomponent elements of aural acoustic immittance as well as to the presence of other otoacoustic emissions (OAEs) in the form of spontaneous otoacoustic emissions (SOEs) and stimulus frequency otoacoustic emissions (SFEs).

It is well accepted that the measured properties of OAEs depend significantly on the normal operation of the middle ear transmission system. Most recently, Kemp et al¹ have discussed thoroughly the influence of the forward and reverse transmission aspects of the middle ear on the amount of sound reaching the cochlea, as well as on the level of sound that returns to the external ear canal. The crucial relationship of emission generation to the integrity of the middle ear transmission system accounts for the fact that most SOEs and the strongest transiently evoked otoacoustic emissions (TEOAEs) are detected in the 1- to 2-kHz region. Because of the known ability of middle ear transmission to affect OAEs, it was reasoned that variables associated with signal conduction may be primary factors in contributing to measured DPE characteristics. Thus, in the present study a detailed evaluation of middle ear functioning, within the limitations of a refined clinical examination, was performed. The comprehensive analysis of aural acoustic immittance in-

cluded testing of various components at various frequencies in order to assess the possibility that borderline defects in the sound conduction mechanism were associated with aberrant DPE patterns. It should be stressed that such detailed investigations of the status of the middle ear were based on an indirect evaluation of its transmission characteristics using measures determined in the outer ear canal. However, the microcomputer-based instrument used represents one of the most sophisticated devices that is currently available for clinical measurement.

Another factor that can influence the production of DPEs is the presence of other OAEs. Since the discovery of OAEs, it has been well recognized that the site-specific responses that Kemp³ termed the "place-fixed" OAEs, including SOEs, SFEs, and TEOAEs, interact with DPEs so that the amplitudes of the latter responses are enhanced significantly. For example, in a recent study in humans of the influence of SOEs on DPE magnitudes, Wier et al⁴ showed that if SOEs were within approximately 50 Hz of the DPE frequency, acoustic distortion products were only about 20 dB smaller than the levels of the eliciting primary tones. Because the typical relationship of DPE to primary-tone levels in humans results in DPEs that are 50 to 60 dB down from the primary tones, it was of interest to investigate whether the coexistence of place-fixed emissions within a given ear influenced, in a general manner, specific aspects of DPE amplitudes or "thresholds" outside the already-noted region of influence (ie, beyond ± 50 Hz of the frequency of a "place-fixed" emission). Evaluating this potential influence was relevant, in particular, for the "irregular" ears showing abnormally large DPEs.

As an indication, moreover, of the ability of the cochlea to generate and conduct reversely propagated responses, it was also of interest to determine if other emission types were present in frequency regions in which DPE "irregularities" had been noted. Thus, by examining the relationship of SOEs and SFEs to the principal properties of corresponding DPEs, we expected to obtain some indication of the cochlea's ability to produce and then conduct signals in a reverse fashion. With the above information on the influence of middle ear functioning and place-fixed emissions on the generation of DPEs, we hoped to gain some insight into the bases of the distinct variations in the pattern of DPE amplitudes with respect to the frequency of stimulation in normal ears.

METHODS

Details concerning the 22 normally hearing subjects have been described completely in a companion report (this Supplement, p 3). Particulars regarding the general experimental protocol involving the testing of aural acoustic immittance and OAEs were also provided in the Table of that report.

ACOUSTIC IMMITTANCE BATTERY

Specialized immittance testing to characterize the middle ear in detail was performed with a commercially available instrument (Virtual Corporation, 310) that was controlled by a personal microcomputer (Apple, Macintosh Plus). The digitally based immittance system, calibrated to read directly in units of acoustic mmhos, permitted a number of tests to be conducted, including standard and advanced multifrequency-multicomponent tympanometry and testing of ipsilateral and contralateral acoustic reflexes at multiple frequencies. The acoustic probe incorporated a solid-state pressure transducer. The various pressure and vacuum conditions were created automatically with a stepper motor and associated cylinder. The immittance system was calibrated daily according to the manufacturer's specified procedures using 0.5-, 2-, and 5-cm³ calibration cavities. For each test frequency, signal magnitude and phase were calibrated simultaneously. Immittance data were stored on-line on microdisk, and hard-copy printouts were provided off-line by a dot matrix printer.

Tympanometry. Standard single-frequency tympanometry was performed with a 226-Hz probe tone at 85 dB sound pressure level (SPL). Air pressure range was adjusted between -300 and $+200$ decapascals (daPa), with sweep direction from minus to plus, and a sweep speed set at a rate of 100 daPa/s, ie, the single-frequency test was completed in about 5 seconds. For multifrequency testing, probe tones were set at 85 dB SPL and air pressure was swept from -300 to $+200$ daPa at 100 daPa/s. The multifrequency sweeps, which were performed in automatic one-sixth-octave steps, took approximately 35 seconds to complete. The outcome of preliminary tests demonstrated that the more detailed testing between 230 and 630 Hz did not provide any more information than was obtained by the standard 226-Hz probe tone in combination with one-third-octave testing between 630 and 1,000 Hz. Consequently, in addition to standard tympanometry, multifrequency testing was performed at 630, 800, and 1,000 Hz by varying the air pressure at each test frequency.

Plotting of tympanograms was performed so that the admittance vector was displayed in both polar and cartesian (rectangular) coordinates to permit magnitude/phase-angle and susceptance/conductance values, respectively, to be analyzed. Tympanograms were displayed as single tracings of admittance magnitude in the compensated format, ie, with the estimate of ear canal volume subtracted from the tympanogram, and phase angle. Susceptance (B) and conductance (G) immittances were calculated automatically from the measurements of admittance magnitude and phase angle. Plots based on rectangular coordinates resulted in the display of

B and G tympanograms as two tracings on the same record.

Parameters that were automatically calculated from the tympanogram on-screen that also appeared on the printed record included peak middle ear pressure, static admittance at the maximum recorded tympanogram value, and an estimate of ear canal volume made at the extreme negative starting pressure, ie, at -300 daPa. An additional factor that was derived from the tympanogram was the pressure gradient difference representing the air pressure interval corresponding to a 50% reduction in peak eardrum admittance. The tympanometric gradient provided a measure of the shape of the tympanogram in the vicinity of the peak.

Immittance tympanograms were defined according to the shape criteria proposed by Liden et al.⁵ and Margolis et al.⁶ Specifically, admittance tympanograms were classified according to the five distinct pressure admittance functions described by Liden et al.,⁵ ie, type A, B, C, D, and E patterns. The bell-shaped type A tympanogram, reflecting the circumstances in which the mobility of the tympanic membrane is greatest when air pressure in the middle ear and ear canal are equal to atmospheric pressure, was typically exhibited by all ears. Types B and C, representing flat and extremely shifted patterns of response, respectively, were never observed among the normally hearing ears of the present study. Tympanograms of the type D pattern, in this series of ears, displayed a small notch of <0.1 mmhos, whereas type E functions demonstrated deeper notching, ie, >0.1 mmhos.

The conductance and susceptance tympanograms were classified according to the multifrequency criteria described by Margolis et al.⁶ This categorization is based on the number of extrema displayed by the tympanograms, with 1G, 3G, and 5G indicating the presence of 1, 3, and 5 peaks, respectively, on the conductance tympanogram. Substitution of the letter "B" for "G" would, then, indicate similar patterns of peaks for the susceptance function. Finally, air pressures were also noted where dips or notches occurred in the admittance, conductance, and susceptance tympanograms in order to assess whether notching between extrema was associated with narrow or broad air pressure extents.

Acoustic Reflex. In evaluating the acoustic reflex for each ear, air pressure was set to the point of maximum admittance, ie, the peak of the tympanogram in response to the 226-Hz probe tone. For eliciting reflexes with ipsilateral and contralateral signal sources, a 1-second pure-tone stimulus with 30-millisecond rise-fall times was varied in 1-kHz intervals from 1 to 2 and 1 to 4 kHz, respectively. A manual screening procedure was used initially to bracket the threshold region. The screening procedure consisted of monitoring the amount of needle

deflection indicated on an on-screen digital meter displaying admittance magnitude as stimulus level was decreased, in 5-dB steps, from about 100 dB hearing level (HL). Once the lowest stimulus level was identified that caused a noticeable needle deflection, an automatic sequence of four intensities, beginning 5 dB below the level that caused the deflection, was presented in descending order. That is, stimulus level was decreased in 5-dB steps beginning at the level that was 5 dB below the approximate threshold level noted on the meter display. For each stimulus level, the reflex waveform was stored on disk for later off-line analyses. Within the 2-second recording interval for each stimulus-level setting, the tone began and ended, respectively, at 0.2 and 1.2 seconds. Consequently, measurements made with respect to signal onset were corrected for the 0.2-second delay.

Single traces of the acoustic reflex waveforms were printed from disk as magnitude plots. Response variables that were calculated from the waveforms included threshold, onset and offset latencies, and the rise and fall times or slope characteristics of the acoustic reflex. Threshold, judged by visual inspection of the record of a given threshold-seeking series, was defined as the stimulus level that elicited a waveform that was at least 20% as large as the maximum waveform tested. The immittance device permitted the video terminal cursor to be moved to any preselected position on the reflex waveform in order to calculate the values of the temporal factors. The timing features were determined on the waveform elicited by the maximum stimulus, which in most cases was around 90 to 95 dB HL. Onset latency was defined as the point in time following stimulus presentation when the reflex reached 10% of its maximum growth, whereas offset latency represented the time after the stimulus was turned off at which the reflex had relaxed to 10% of its maximum amplitude. Rise and fall times were determined on the corresponding slopes of the reflex tracing as the time interval in which the curve rose or fell, respectively, to 50% of its maximum amplitude. The time periods in which the reflex waveform crossed the selected 10% and 50% growth and decline points were determined by moving the cursor to appropriate prereponse and postresponse baselines and to positions representing the visually determined initial and terminal maximum growth magnitudes. By use of the x-axis scale, displaying the duration of the 2-second recording period labeled in 20-microsecond coordinates, the time periods associated with these points were read directly from the printed record. The appropriate percent magnitude values were then calculated from these measures and the corresponding response latencies determined.

OTOACOUSTIC EMISSIONS

Spontaneous Otoacoustic Emissions. During each

of the two test sessions, examinations for SOEs were performed in the absence of intentional stimulation by use of the DPE-measuring equipment described in the previous companion report (this Supplement, p 3). The SOE system consisted of a microphone (Etymotic Research, 10-A), a measuring amplifier (Bruel and Kjaer, 2620), a dynamic signal analyzer (Hewlett-Packard, 3561A), and a plotter (Hewlett-Packard, 7470A). Spectra of the ear canal sound pressure based on 30 averages were collected from 0.8 to 7.4 kHz by use of a bandwidth of 3.75-Hz and 1-kHz frequency windows, each overlapping the previous window by 200 Hz (0.8 to 1.8 kHz, 1.6 to 2.6 kHz, etc). An SOE was defined as a spectral peak 3 dB or greater above the noise floor on at least two consecutive sweeps of the same frequency range. For each SOE, the peak frequency and amplitude were recorded.

Stimulus Frequency Otoacoustic Emissions. The SFEs were detected by a heterodyne analyzer (Bruel and Kjaer, 2010) with bandwidth set to 3.16 Hz, and use of a multilevel stimulation procedure. The output of the analyzer's beat frequency oscillator was connected to one of the insert earphone transducers (Etymotic Research, 2), and the sound pressure measured in the ear canal by the microphone system was the input signal to the analyzer. The analyzer's output was plotted by an associated x-y recorder (Hewlett-Packard, 7015B). Before measurements were acquired, the output of the analyzer was calibrated to a standard 50-dB SPL tone at 1 kHz that was presented to each ear of a given subject.

Emissions were measured by stimulation with a continuous pure tone that was swept slowly from 0.4 to 2 kHz over a 2-minute period in single-level sweeps separated by 10-dB steps, beginning at 50 dB SPL and descending to 20 dB SPL. Stimulus frequency emissions, in response to stimulation by 20-dB SPL tones, were identified as regularly occurring oscillations of the emission tracing. On the basis of empiric observations, the perturbations were classified as SFEs if the interpeak frequency distance was at least 25 Hz and the amplitude was 1 dB or greater. For purposes of quantification, we chose to define all single peaks in the ear canal sound pressure record that satisfied the above criteria as SFEs.

Adjacent peaks probably arise from a continuous segment of basilar membrane encompassing a particularly strong region of biomechanical activity. Moreover, it is likely that only two or three such areas exist within a given cochlea. However, within these active regions, multiple internal reflections, along with various numbers of actual impedance discontinuities, result in complex processes that produce in-phase and out-of-phase emission energy that enhances or diminishes the level of the swept stimulus as it is measured in the ear canal. The procedure of counting individual peaks as SFEs seemed

justifiable as a first-order approximation of the amount of activity within a given ear, in that the overall extent of the region of biomechanical enhancement would be expected to increase the number of perturbations produced.

Variables measured from the SFE record in response to the lowest stimulation level at 20 dB SPL included 1) the number of peaks and, to permit calculation of the frequency intervals between adjacent peaks, the corresponding frequencies at which the periodic fluctuations in acoustic energy occurred, and 2) the peak-to-peak amplitudes in decibels. These latter measures, summing the maximum upward and downward fluctuations of the ear canal SPL, provided estimates of SFE amplitude. The analog system used to analyze SFEs did not permit the influence of the sound system on response properties to be automatically removed from the record. Instead, the response elicited by 50-dB stimuli, known to be influenced primarily by sound system properties, was used to interpret the form of the SFE record in which the response was dominated by the evoked emissions, ie, in response to 20-dB SPL stimuli.

RESULTS

ACOUSTIC IMMITTANCE

The acoustic immittance testing was performed with an instrument that is relatively new to the field. Consequently, it seemed reasonable to first consider the average immittance values determined with this device before relating them to the generation of DPEs. In this manner, measurements from the 44 ears of the present study could be evaluated with respect to normal data reported in the literature that were obtained with more conventional instruments. In particular, data points in response to 226-Hz tones were compared to readings acquired by well-standardized clinical equipment, whereas measurements elicited by higher-frequency probe tones were related to the results of more advanced tests. Before detailing the results of the aural acoustic immittance testing, however, it is important to note that when the data were statistically analyzed (two-tailed Student's *t* test), no significant asymmetries were noted between the right and left ears of the subjects. Similar analyses of gender differences indicated that only the estimated volume of the outer ear canal achieved statistical significance, with men possessing larger volumes at all probe frequencies tested. On average, such ear canal volumes varied in approximated size for women and men from 0.93 and 1.15 mmhos ($p < .05$), respectively, at 226 Hz, to 3.7 and 4.6 mmhos ($p < .005$), respectively, at 1 kHz.

Tympanometry. The values listed in Table 1 represent the average ($n = 44$) data (± 1 SD) for each of the variables studied by tympanometry. Each row of data depicts the value of the designated immit-

TABLE 1. AURAL ACOUSTIC IMMITTANCE

	226 Hz	630 Hz	800 Hz	1,000 Hz
Peak middle ear pressure (daPa)	4.00 (± 12.00)	20.00 (± 11.00)	24.00 (± 13.00)	31.00 (± 13.00)
Static immittance (mmhos)	0.78 (± 0.57)	0.80 (± 0.73)	1.75 (± 1.07)	3.97 (± 2.27)
Estimated ear canal volume (mmhos)	1.05 (± 0.37)	0.44 (± 0.11)	1.25 (± 0.47)	4.19 (± 1.13)
Susceptance (mmhos)	1.58 (± 0.77)	0.60 (± 3.00)	2.26 (± 4.69)	4.05 (± 9.98)
Conductance (mmhos)	1.02 (± 0.42)	1.62 (± 1.54)	7.01 (± 3.81)	11.27 (± 8.85)
Gradient pressure difference (daPa)	78.4 (± 32.20)	75.1 (± 35.90)	90.4 (± 45.00)	117.4 (± 56.90)
Phase angle ($^{\circ}$)	57.2 (± 15.60)	11.8 (± 46.00)	-10.2 (± 19.70)	5.0 (± 21.40)

tance component with respect to the standard probe frequency at 226 Hz, along with the corresponding values for the higher frequencies at 630, 800, and 1,000 Hz. Except for measures of phase angle, it is clear that responses to the 630-Hz probe tone varied minimally from those recorded at 226 Hz. Thereafter, however, the absolute values of the parameters tended to increase in magnitude as probe frequency increased. Notwithstanding this trend, the range of variability indicated by the extents of the related ± 1 -SD indicators obscured in general any significant differences between readings in response to the various probe tone frequencies.

The results of analyses classifying the multifrequency admittance, conductance, and susceptance tympanograms are presented in Table 2. Inspection of these values, showing the percentage of the typical tympanometric patterns at the different probe frequencies, reveals that the data are in accordance with the multifrequency findings of other investigators.^{5,6} Thus, for all three immittance components in general, as probe frequency increased, the number of more complex tympanograms represented by the D and E admittance classification patterns and the 3G/5G and 3B/5B conductance and susceptance types, respectively, also grew. Conversely, with the increase in tympanogram complexity, a corresponding reduction in the number of single-peaked functions occurred with respect to the type A admittance, 1G conductance, and 1B susceptance tympanograms.

Acoustic Reflexes. Table 3 presents the average data acquired by the aural reflex testing procedures. One important feature that describes these measurements is that in most cases, in response to 1-kHz reflex-activating tones the ipsilateral or uncrossed reflexes demonstrated values that were lower than those associated with the crossed reflexes. However, when data points for the uncrossed reflexes were omitted, although some trends were apparent (eg, rise times tended to be shorter for low than for high probes), increases in the eliciting frequency did not appreciably alter the timing properties of the reflex. Analysis of the acoustic reflex parameters using conventional correlational tests (ie, Pearson product-moment correlation coefficients) indicated that thresholds were related for both uncrossed reflexes at 1 and 2 kHz ($r = .70$, $p < .0001$) and crossed reflexes at 1, 2, 3, and 4 kHz (r ranging

from .40 to .79, p ranging from $< .01$ to $< .0001$).

Influence of Immittance Variables on DPEs. One goal of the present investigation was to determine if detailed immittance data from the 44 normally hearing ears could account for a portion of the variability observed in DPE amplitudes. In addition, an attempt was made to determine if this information could be related specifically to the 15 irregular ears that showed either deficient or enhanced DPEs within restricted frequency regions. Initial analyses performed correlations between all DPE test frequencies and all immittance measures. This treatment of the data resulted in a few significant but probably spurious correlations. Thus, an attempt was made to simplify the data without obscuring relevant relationships. This objective was accomplished by calculating a mean DPE measure for each ear by averaging DPE amplitudes in response to 75-dB SPL primaries at 1, 2, 4, 6, and 8 kHz. The averaging procedure was justified because prior testing revealed that across test frequencies, DPE amplitudes were significantly correlated (this Supplement, p 3). Moreover, because comparable analyses reported above indicated that thresholds for crossed and uncrossed reflexes were also strongly related, a similar analysis was performed for these measures in order to derive mean crossed and uncrossed reflex thresholds for each ear. Despite the application of these data reduction techniques, subsequent correlational analyses performed between all DPE and reflex scores failed to reveal any significant relationship between DPE amplitudes and acoustic reflex thresholds or timing features, includ-

TABLE 2. PERCENTAGES OF EACH TYMPANOGRAM TYPE AT DIFFERENT PROBE FREQUENCIES

	226 Hz	630 Hz	800 Hz	1,000 Hz
Admittance				
Type A	84	78	75	50
Type D	16	11	5	18
Type E	0	11	20	32
Susceptance				
1B	86	82	61	70
3B	14	18	18	30
5B	0	0	21	0
Conductance				
1G	86	82	30	50
3G	12	18	32	50
5G	2	0	38	0

TABLE 3. ACOUSTIC REFLEX

	<i>Ipsilateral</i>		<i>Contralateral</i>			
	1 kHz	2 kHz	1 kHz	2 kHz	3 kHz	4 kHz
Threshold (dB HL)	80 ($\pm$ 7)	86 ($\pm$ 7)	84 ($\pm$ 8)	84 ($\pm$ 9)	85 ($\pm$ 9)	91 ($\pm$ 11)
On latency (ms)	180 ($\pm$ 70)	160 ($\pm$ 60)	180 ($\pm$ 90)	160 ($\pm$ 80)	190 ($\pm$ 100)	170 ($\pm$ 110)
Rise time (ms)	290 ($\pm$ 90)	300 ($\pm$ 70)	320 ($\pm$ 90)	340 ($\pm$ 70)	360 ($\pm$ 100)	350 ($\pm$ 120)
Fall time (ms)	1,210 ($\pm$ 30)	1,200 ($\pm$ 50)	1,220 ($\pm$ 40)	1,210 ($\pm$ 30)	1,210 ($\pm$ 40)	1,220 ($\pm$ 40)
Off latency (ms)	1,310 ($\pm$ 70)	1,330 ($\pm$ 100)	1,350 ($\pm$ 60)	1,370 ($\pm$ 100)	1,370 ($\pm$ 100)	1,360 ($\pm$ 90)

ing onset and offset latencies and rise and fall times.

The average DPE amplitudes were also compared to the individual tympanometric measures, and again, in general no significant findings were uncovered. However, for the two ears displaying enhanced high-frequency DPEs, the measures of estimated ear canal volume and pressure gradient difference were ≥ 2 SDs from the average values. This outcome suggested that a hypermobile middle ear conduction apparatus was responsible for the augmented DPEs occurring between 5 and 8 kHz in both ears of the one "irregular" subject demonstrating this peculiarity. However, for the remaining 13 "irregular" ears exhibiting diminished DPEs within limited frequency ranges, an association between DPE amplitudes and tympanometric responses was not observed. This general lack of a relationship is best illustrated by the results of statistically comparing the DPE levels to a measure of the mobility of the middle ear's signal transduction system, such as static admittance, which resulted in a typical non-significant finding, ie, $r = .03$ ($p > .87$).

In an attempt to satisfy the second goal of determining if subjects with "irregular" DPE frequency patterns differed from individuals with "regular" DPE patterns with respect to measures of middle ear function, separate statistical tests (t tests) were performed between the findings for the two categories of subject. These comparisons indicated that DPE amplitude, tympanometric parameters, and acoustic reflex thresholds did not differ between the two groups of subjects. Statistical comparisons were not carried out for the individual subtypes of the "irregular" group (ie, low-, middle-, and high-frequency losses or the high-frequency-enhanced pattern) and "regular" subjects, because of the small number of subjects available in the former subgroups and the large number of t tests that would be required to complete the analysis. Results like these suggest that in ears exhibiting normal hearing, slight variations in acoustic immittance variables as measured clinically cannot account for the DPE differences observed in these ears.

OTOACOUSTIC EMISSIONS

Spontaneous Otoacoustic Emissions. In the previous study (this Supplement, p 3), it was noted that 13 subjects (60%) demonstrated SOEs in 21 of their 44 ears (48%). Further, 8 (60%) of the 13 subjects exhibiting SOEs had emissions in both ears, so that

SOEs were measured in 80% of the ears of spontaneously emitting individuals. Of the 21 ears with SOEs, 18 (86%) demonstrated two or more emissions, with each ear emitting four on average. In support of the observations of other investigators that female ears emit more SOEs than male ears (eg, Strickland et al⁷), 7 (70%) of the 10 women and 6 (50%) of the 12 men of the present study demonstrated SOEs. In further support of the propensity of female ears to show SOEs, all 7 (100%) spontaneously emitting women demonstrated SOEs bilaterally, whereas only 1 (17%) of the 6 emitting men showed bilateral SOEs. The SOE frequencies ranged from about 800 Hz to 7 kHz, with amplitudes distributed between -17 and 15 dB SPL. The plots of Fig 1 provide more detailed information concerning the distribution patterns for the frequencies and amplitudes of the measured SOEs.

Stimulus Frequency Otoacoustic Emissions. Stimulus frequency emissions were recorded in all 44 ears. Each ear, on average, emitted seven SFEs, ie, each SFE trace exhibited seven discrete maxima. The numbers of SFEs in right (mean = 6.6) and left (mean = 7.3) ears were similar. In addition, there was a tendency for the numbers of SFEs in the ears of a specific individual to be related, but this trend did not reach statistical significance. The plots of Fig 2 illustrate the distribution patterns of SFE frequencies and amplitudes. It is clear from Fig 2A that within the 1.6-kHz test span extending from 0.4 to 2 kHz, the majority of SFEs occurred between about 0.7 and 1.4 kHz. Inspection of the SFE records elicited by the highest level of stimulation at 50 dB SPL showed that the sound system decreased, on average, by a few decibels at 1.5 kHz and by about 4 dB at 2 kHz. It is plausible that the falloff in sound levels toward the higher extent of the test range contributed to the decrease in SFEs noted for frequencies over 1.5 kHz. However, other evidence presented below concerning SFE amplitudes over the 1.5- to 2-kHz frequency extent suggests that the associated decrease in sound system output did not greatly influence the amplitudes of SFEs over 1.5 kHz.

Data illustrated in Fig 2B indicate that the predominate peak-to-peak amplitudes for detected SFEs were between about 2 and 3 dB. In fact, the average SFE amplitude across all ears was 3.3 dB, with right and left ears emitting SFEs of approximately the same amplitude. However, there was no

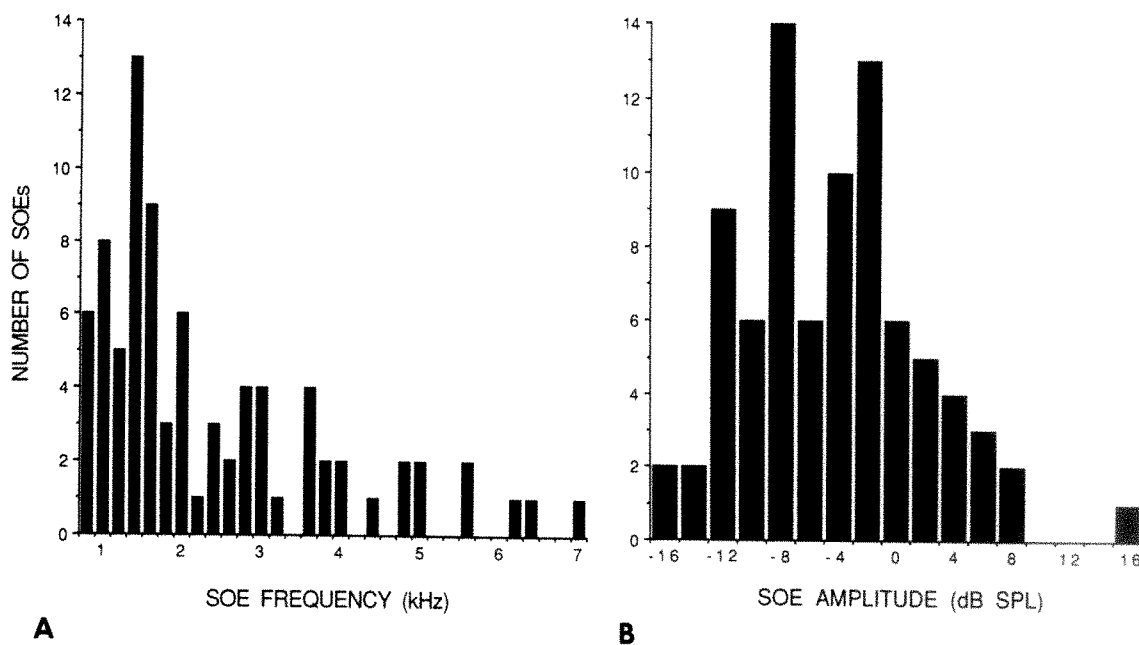


Fig 1. Spontaneous otoacoustic emissions (SOEs). A) Frequency distribution of SOEs in 21 ears exhibiting these emissions. Note that mode of SOE distribution occurred between 1.4 and 1.6 kHz. B) Amplitude distribution of same SOEs. Note that predominant SOE amplitudes were between -2 and -8 dB sound pressure level.

significant association between SFE magnitudes for both ears of a given subject.

Because SOEs and SFEs both represent types of place-fixed emissions,³ it was of interest to determine if any relationships existed between the two emission classes. Statistical comparisons (two-tailed *t* test) of the numbers of SFEs between ears that exhibited SOEs and those that did not showed that ears with SOEs had significantly ($p < .05$) more SFEs (mean = 8.3) than ears without SOEs (mean =

5.6). However, correlational analyses between the number of SOEs within each ear exhibiting SOEs and the corresponding number of SFEs failed to reveal any association between the two emission types. That is, for any one individual, within a given ear there was no relationship between the number of SOEs and the corresponding number of SFEs. When SFE amplitudes between ears with and without associated SOEs were compared, a statistically significant ($p < .005$) difference occurred in that SFEs in ears also exhibiting SOEs were larger

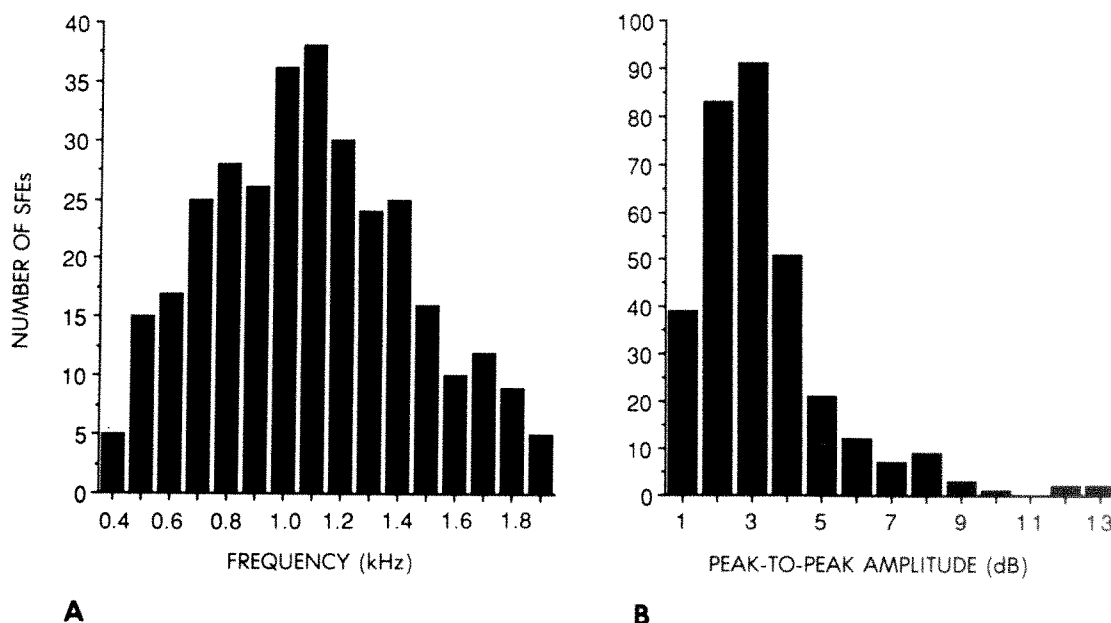


Fig 2. Stimulus frequency emissions (SFEs). A) Frequency distribution of SFEs displayed by all 44 ears. Note that majority of SFEs occurred between 0.7 and 1.4 kHz. B) Amplitude distribution of same SFEs. Note that predominant peak-to-peak SFE amplitudes were between 2 and 3 dB.

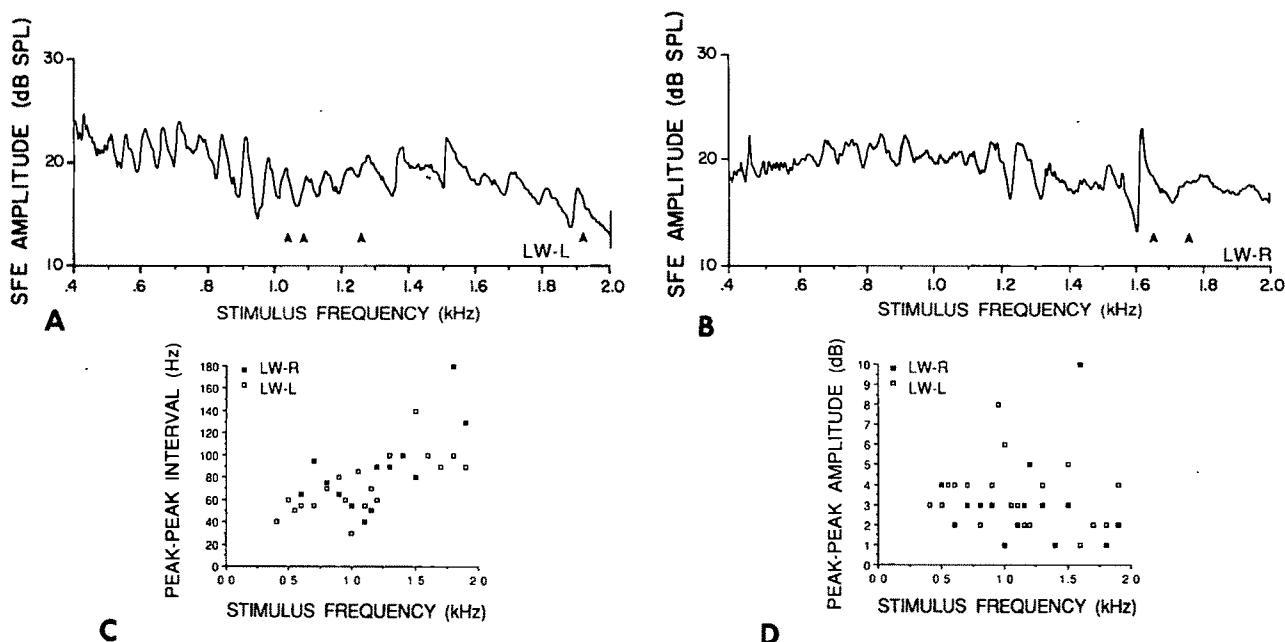


Fig 3. (Subject LW) A,B) Stimulus frequency emissions (SFEs) in A) left and B) right ears, with spontaneous otoacoustic emissions (arrowheads). Note regular fluctuations reflecting definitive peaks and valleys as stimulus frequency increased. C) Distribution of peak-to-peak frequency intervals for both ears. D) Distribution of peak-to-peak amplitudes across frequency for both ears.

(mean = 3.9 dB) than those measured in ears not displaying SOEs (mean = 2.7 dB).

The plots of SFEs for the individual ears illustrated in Figs 3 and 4 provide examples of the influence of SOEs on the generation of SFEs. Figure 3 depicts quite robust SFEs from the left (Fig 3A) and right (Fig 3B) ears of a subject having several corresponding SOEs (arrowheads). In the ear with the most SOEs (Fig 3A), over 20 individual SFE peaks could be discerned, whereas the contralateral ear

(Fig 3B), showing fewer SOEs, also exhibited fewer SFEs (< 20). The quantitative plots of Fig 3C,D illustrate, respectively, the peak-to-peak frequency intervals and the peak-to-peak amplitudes of the SFEs for both ears. Inspection of these data reveals that as frequency increased in linear units, the frequency separation between SFEs increased. Thus, whereas the peak-to-peak separation of SFEs around 0.5 kHz was about 50 to 60 Hz, by 1.5 kHz this distance had increased to approximately 100 Hz. Simple regression analysis confirmed that this

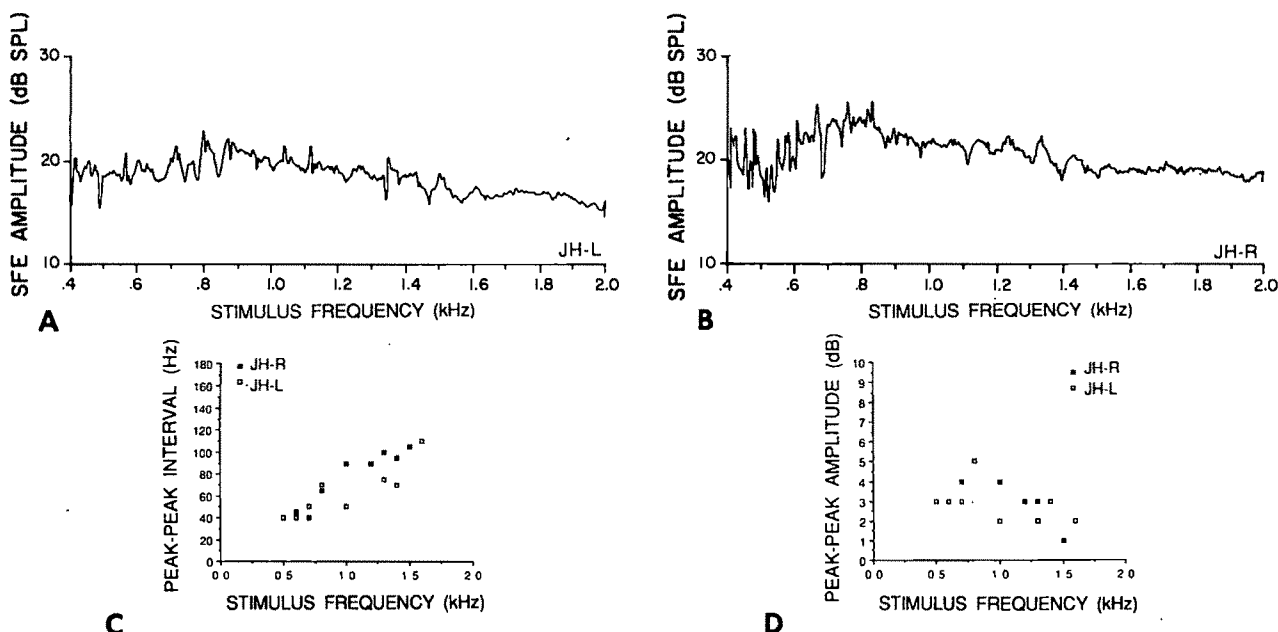


Fig 4. (Subject JH) A,B) Stimulus frequency emissions (SFEs) in A) left and B) right ears, without spontaneous otoacoustic emissions. C) Distribution of peak-to-peak intervals with respect to stimulus frequency for both ears. D) Distribution of peak-to-valley amplitudes over frequency for both ears.

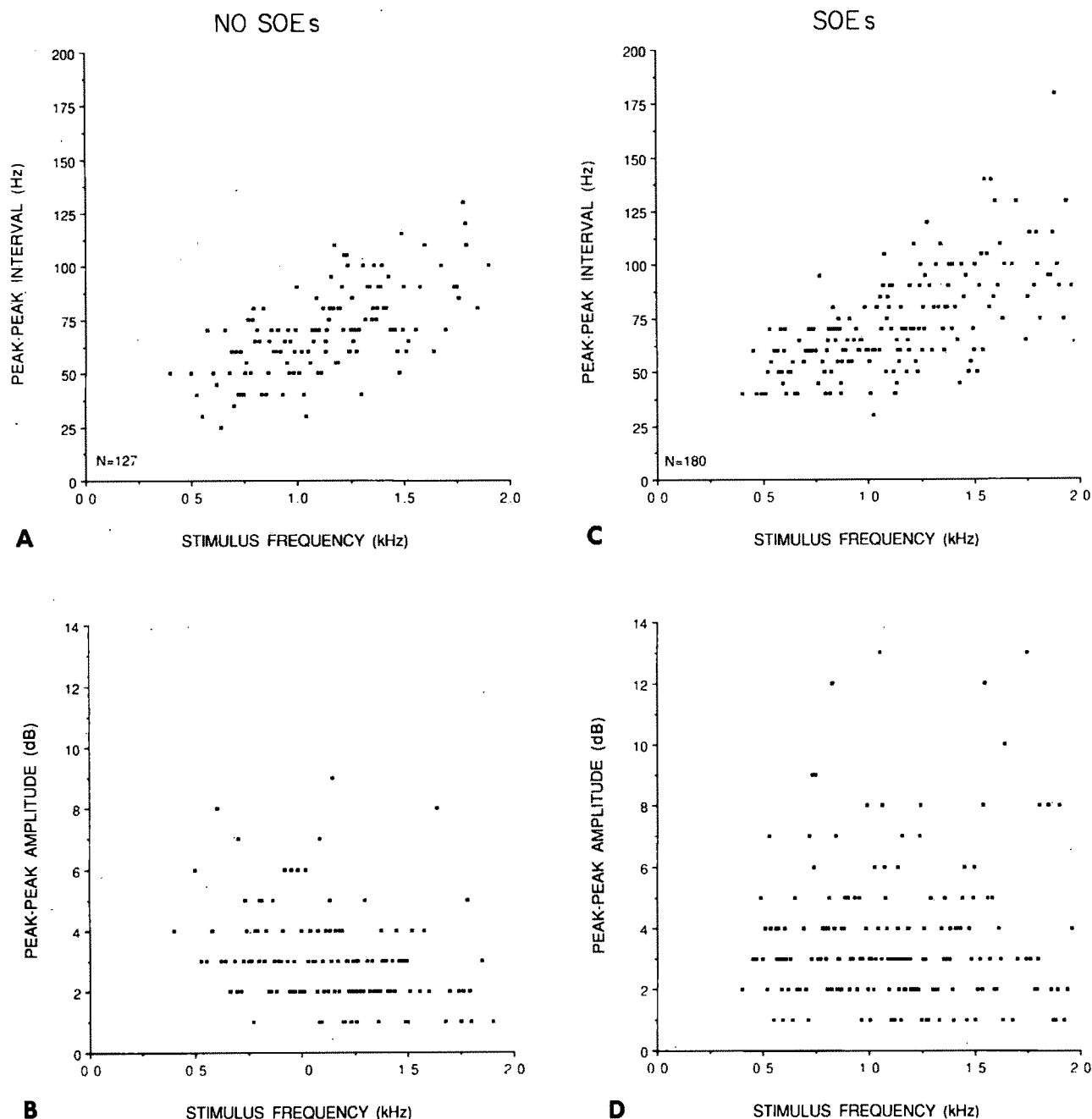


Fig 5. Stimulus frequency emissions (SFEs) across all 44 ears. Scatterplots relate SFE peak-to-peak frequency intervals (top) and amplitudes (bottom) to stimulus frequency for A,B) non-spontaneous otoacoustic emission (SOE) ears and C,D) SOE ears.

apparent trend was best fit by a straight line ($r = .68$) indicating that for subject LW, for every 100-Hz increase in SFE frequency, peak separation increased by 4 Hz.

The scatterplot of Fig 3D comparing SFE amplitude to emission frequency depicts rather accurately the outcome of a similar regression analysis of this relationship. Clearly, in these two spontaneously emitting ears, no strong association ($r = .01$) existed between the two variables. Thus, as SFE frequency increased, SFE magnitude stayed approximately the same at 1 to 4 dB.

The plots of Fig 4 illustrate graphical representations of similar analyses performed on the two ears of another subject, who exhibited SFEs in the absence of SOEs. In comparing the topography of the SFE records for either ear and those of the spontaneously emitting ears of Fig 3A,B, it is obvious that the peaks and valleys representing the SFEs of the former ears were less pronounced than those of the latter individual. In addition, it is clear that the ears without SOEs emitted fewer SFEs. The scatterplots of Fig 4C,D depict the relationship between emission frequency and the frequency spacing between SFEs and their amplitudes, respectively.

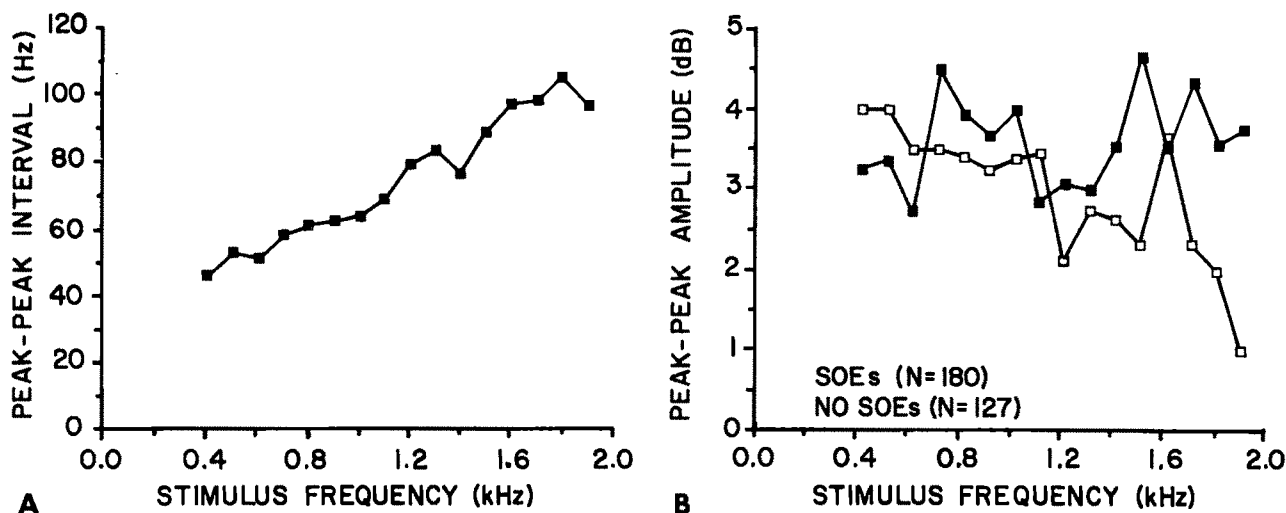


Fig 6. Graphs showing stimulus frequency emission (SFE) parameters describing peak-to-peak A) intervals and B) amplitudes with respect to stimulus frequency. In B, SFE amplitudes in ears with spontaneous otoacoustic emissions (SOEs) (solid squares) and without SOEs (open squares) are compared.

These data reveal that the growth in frequency distance between SFE peaks, as frequency increased, was similar to that described for spontaneously emitting ears, ie, about a 5-Hz increment in the peak-to-peak separation for every 100-Hz increase in emission frequency ($r = .87$). In contrast to the observation that SFE amplitudes in ears that also emitted SOEs remained relatively constant across emission frequency, the data in Fig 4D illustrate that for these ears with no SOEs, SFE amplitudes decreased as emission frequency increased. Thus, for the ears of subject JH, for every 100-Hz increment in SFE frequency, emission amplitude decreased about 0.5 dB ($r = .91$).

The trends noted above for SFEs in individual ears were substantiated across all 44 ears. The population results are illustrated in the plots of Fig 5, in which the peak-to-peak frequency distances and amplitudes of SFEs are displayed for ears that also emitted SOEs (right) and for those that had no SOEs (left). Simple regression analyses confirmed the majority of the findings illustrated above for the individual ears. Thus, the resulting straight-line fits, which were essentially identical for ears with and without SOEs, ie, $r = .65$ and $r = .66$, respectively, indicated that the peak-to-peak distance interval grew about 4 to 5 Hz for every 100-Hz increase in emission frequency. However, although SFE magnitudes in ears with coexisting SOEs remained relatively constant across frequency ($r = .03$), there was a slight tendency for amplitudes in ears without SOEs to decrease as emission frequency increased ($r = .29$).

The group patterns described above are illustrated more clearly in the line graphs of Fig 6. In Fig 6A, only one curve is shown representing the increase in frequency distance, in hertz, between SFE peaks as emission frequency grew, because the data (mean ± 1 SD) describing this relationship were es-

entially identical in both SOE and non-SOE ears. Close inspection of the graph indicates that between approximately 400 and 1,800 Hz, the peak-to-peak intervals between SFEs increased from about 50 to 110 Hz. The plot of Fig 6B illustrates amplitude curves for both SOE and non-SOE ears. It is clear from examination of these data that the amplitudes of SFEs tended to remain relatively constant, on average, in ears exhibiting SOEs (solid squares), whereas a tendency for SFEs to grow smaller as emission frequency was raised was apparent for ears without corresponding SOEs (open squares).

To test the direct influence of SOEs on SFEs, the amplitudes of SFEs, both within (ie, 1 to 100 Hz) and outside (ie, > 100 Hz) the frequency ranges of SOEs, were examined in ears exhibiting SOEs. In general, SFEs that were close to SOEs demonstrated significantly increased amplitudes (t test, $p < .001$). That is, SFEs in regions associated with SOEs displayed mean amplitudes of 5.3 dB, whereas those in non-SOE areas exhibited average magnitudes of only 3.3 dB. However, when the amplitudes of related pairs of SOEs and SFEs (ie, emissions that were within 100 Hz of each other) were directly compared, there was no obvious influence of SOE magnitudes on SFE levels ($r = .18$).

Influence of SOEs and SFEs on DPEs. A major aim of the investigation was to examine the influence of SOEs and SFEs on DPEs for all ears, with special attention given to those ears demonstrating DPE irregularities. The numbers of SOEs and SFEs were compared statistically to the magnitude of the DPEs in response to 75-dB SPL primaries and their "thresholds" at 1, 2, 4, 6, and 8 kHz (see this Supplement, p 3, regarding the rationale for choosing these specific variables). In general, the presence of SOEs within the DPE test range failed to correlate with DPE amplitude or "threshold" at any of the DPE frequencies examined. Similar analyses be-

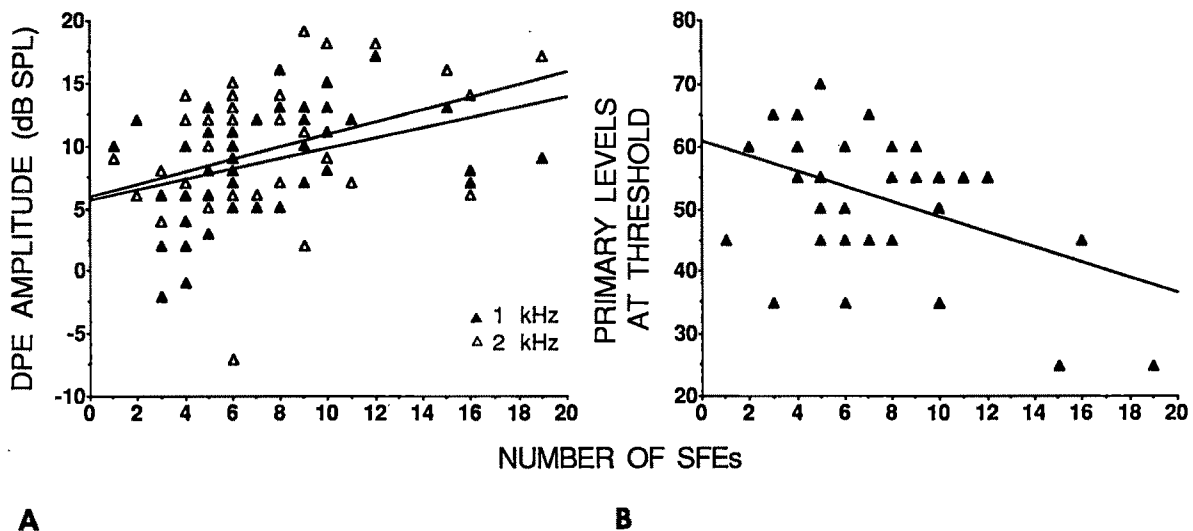


Fig 7. Influence of number of stimulus frequency emissions (SFEs) on distortion product emission (DPE) "thresholds" and amplitudes. Straight lines represent best fit to data points based on simple linear regression analysis. A) Scatterplot showing that as number of SFEs increased, DPE amplitudes at 1 kHz (solid triangles) and 2 kHz (open triangles) increased in response to 75-dB SPL primaries. B) Scatterplot showing that as number of SFEs increased, DPE "thresholds" at 1 kHz decreased.

tween the number of SFEs and DPE amplitudes and "thresholds" demonstrated that DPE amplitudes at 1 kHz ($r = .37$, $p < .05$) and 2 kHz ($r = .37$, $p < .05$) were significantly correlated with the number of SFEs in a given ear. Additionally, DPE "thresholds" at 1 kHz ($r = .46$, $p < .005$) also depended upon the number of SFEs present. These findings are depicted in the scatterplots of Fig 7A,B, respectively.

Other comparisons were carried out to determine if ears classified as "irregular" differed from those belonging to the "regular" group in terms of the number of SOEs or SFEs. Specifically, χ^2 analysis revealed that the number of individuals with SOEs did not differ between the two groups of subjects. With respect to individual ears, the mean number of SOEs per ear was also not significantly different between subjects exhibiting the two general types of DPE frequency patterns. A similar comparison revealed no difference between the number of SFEs per ear for "irregular" compared to "regular" ears. Thus, measures of other OAEs, which included SOEs and SFEs, failed to explain the presence of restricted regions of low-amplitude DPEs in approximately one third of normal ears.

Several individual examples of the relationship of these other emission types to the irregularities in DPE generation are shown in Figs 8 and 9. These examples substantiate the inability of other emission types to account for low-amplitude DPEs. In Fig 8B, for one subject, a repeatable SOE at 2.8 kHz is shown that clearly was generated within a frequency region in which DPE amplitudes, as shown by the individual's DPE "audiogram" illustrated in Fig 8A, were close to the boundary described by the noise floor of the measuring system. This finding is consistent with normal middle ear conduction and

also suggests that the cochlear mechanisms required for place-fixed emission generation were operating normally within the same frequency region. Figure 9 illustrates similar data from another subject who showed low-amplitude SFEs within the frequency region in which DPE amplitudes were essentially equivalent to noise floor levels, ie, from 1 to 1.5 kHz.

Although it appeared that the presence of SOEs, in general, did not influence the thresholds and amplitudes of even the lower-frequency DPEs, when individual subjects demonstrating more than a few SOEs in each ear were examined several interesting properties were revealed. The DPE "audiogram" and input-output (I/O) functions of Fig 10 illustrate these observations. For example, for this individual having three SOEs (1.655 to 2.539 kHz) in the right ear and eight (1.030 to 3.678 kHz) in the left, at all levels and all frequencies tested the DPE "audiograms" tended to be at the maximum limit of the $+1$ -SD range of amplitudes described for the average ear. Moreover, the finding of rather large-amplitude DPEs in ears with numerous SOEs was supported by the similar robust emissions observed at the individual I/O test frequencies illustrated below. Another feature revealed by the individual I/O functions of ears with a number of SOEs was that the shapes of the curves tended to be more complex than those for ears without any or with few SOEs. Thus, the function could bend over, as manifested by the DPE I/O for the right ear (open squares) at 2 kHz, or it could display a notch in its growth pattern in response to moderate-level primaries, as indicated for the left ear (solid squares) at 4 kHz. However, it is important to stress that ears in which medium-level primary tones elicited such focused reductions in DPE amplitudes, in the form of

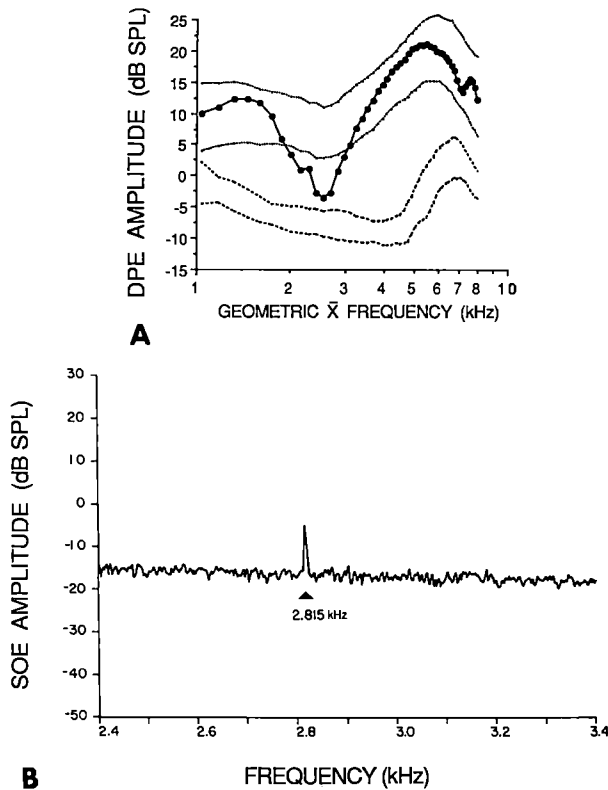


Fig 8. (Subject MF) Spontaneous otoacoustic emissions (SOEs) and distortion product emissions (DPEs) in left ear. A) DPE "audiogram" elicited by 75-dB SPL primaries showing decrement in emission amplitudes between 2 and 3 kHz. B) SOE tuned to 2.815 kHz in region of reduced DPEs, indicating that emissions can be generated in this frequency region.

notches and bend-overs, did not contribute to the "irregular" categorization of DPE amplitudes over frequency. This lack of association occurred because the latter classification scheme was based on DPE amplitudes in response to 75-dB SPL tones, and neither bend-overs nor notches were usually apparent in the I/O functions at this level of stimulation. Finally, the detection "thresholds" in ears with many SOEs appeared to be lower than normal. For example, in Fig 10, the thresholds at 4 and 5 kHz for the left ear were clearly more sensitive than those described for the majority of normally hearing subjects. It is also interesting that the threshold enhancement effect was noted especially for frequency regions in which SOEs were not measured. This finding suggests a more general influence of SOE enhancement of DPE responses over frequency ranges that were greater than the ± 50 -Hz effects observed by previous investigators.⁴

DISCUSSION

The primary purpose of the present study was to evaluate the contribution that some aspects of the cochlear and middle ear generation and/or transmission systems made to the major features of DPE generation in a population of normal ears, including detection "threshold" and magnitude, in re-

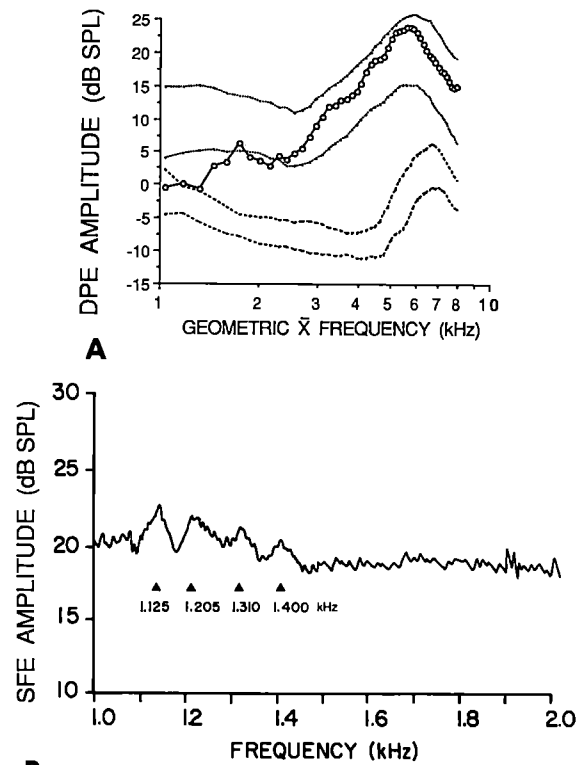


Fig 9. (Subject MW) Stimulus frequency emissions (SFEs) and distortion product emissions (DPEs) in right ear. A) DPE "audiogram" elicited by 75-dB SPL primaries showing reduced emissions between 1 and 1.6 kHz. B) SFEs (arrowheads) detected in identical frequency region.

sponse to 75-dB SPL primaries. A focused investigation of these variables constituted a first step toward understanding the source(s) of the considerable variability in DPE magnitudes observed in normally hearing humans (this Supplement, p 3). Toward this end, in an effort to examine middle ear function and to determine if subtle differences in immittance, as revealed by sophisticated clinical testing, caused the observed deficits in DPE amplitude, especially for low- and middle-frequency DPEs, the middle ear's signal transmission capability was assessed by use of comprehensive tests of aural acoustic immittance. In addition, as an indication of the generation and/or conduction properties of the cochlea and middle ear, the influence of SOEs and SFEs on DPE generation was also investigated in detail.

Several studies have assessed the effects of manipulating the stiffness of the tympanic membrane and ossicular chain on emission generation by altering the air pressure in the external canal or changing body posture⁸⁻¹⁰ or activating the acoustic reflex.^{10,11} These tactics resulted in slight increases in emission frequency along with reductions in amplitude, thus indicating that changes in the middle ear transmission of cochlear emissions can affect their detectability in the external ear canal. Thus, to assess the contribution that middle ear functioning makes to DPE generation, multi-probe frequen-

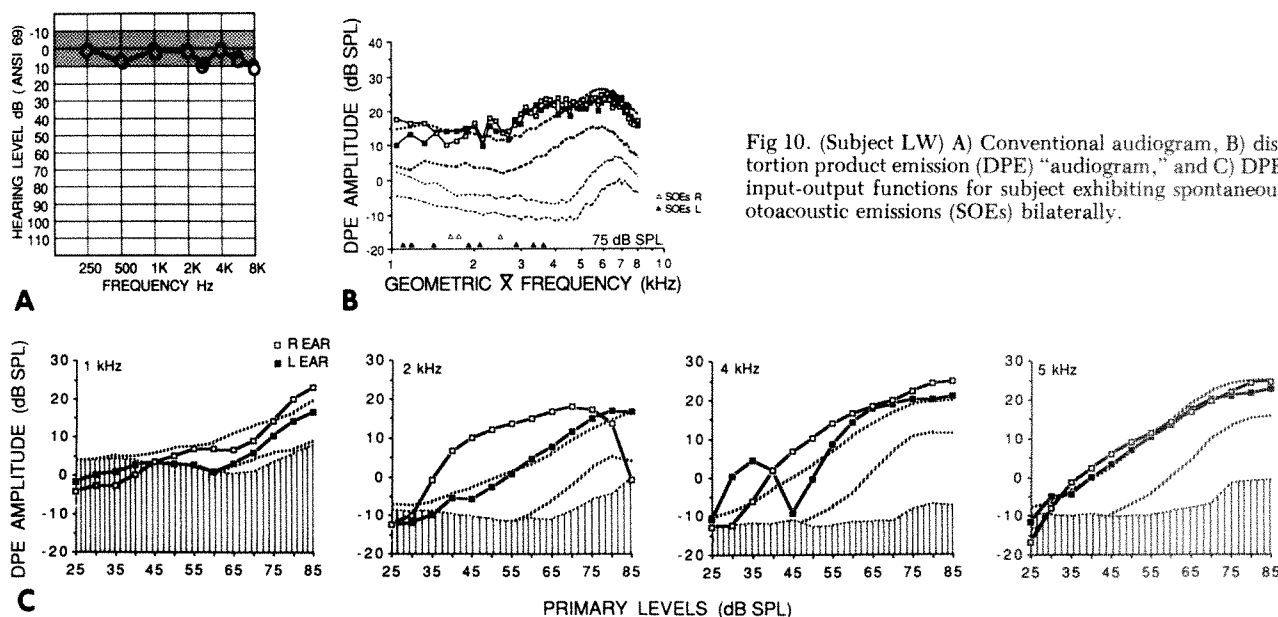


Fig 10. (Subject LW) A) Conventional audiogram, B) distortion product emission (DPE) "audiogram," and C) DPE input-output functions for subject exhibiting spontaneous otoacoustic emissions (SOEs) bilaterally.

cy testing was used, both to optimize the distinction between normal and possibly abnormal middle ear transmission and to evaluate the conduction portion of the hearing mechanism over a reasonable extent of its normal range of operation. Such rigorous testing indicated that the middle ear conduction apparatus was clinically normal in the 44 ears examined here. Subsequent correlational analyses, moreover, revealed that at this level of sensitivity the normal variations in the tympanometric or acoustic reflex properties of a given ear did not contribute significantly to DPE amplitudes. For example, the interactions of the probe tones with the resonances of the middle ear, detected by measures of phase angle, were not related very critically to the amplitudes of DPEs. Further, although other immittance measures, including static immittance, conductance, susceptance, pressure gradient, and estimated ear canal volume, changed in response to higher probe frequencies, none of these factors were associated significantly with the observed DPE properties. Previous work showing that emissions were larger in children than in adults^{7,12} supported the expectation that smaller ear canal volumes would be associated with larger-amplitude DPEs. In fact, the only individual showing mechanical overactivity in the form of enhanced high-frequency DPEs also had the largest estimates of ear canal volume — a relationship that was in contrast with the expected association.

Little information is available about the effects of higher probe-tone frequencies on immittance variables. However, the orderly sequence reported here with respect to the systematic increase in the complexity of admittance, conductance, and susceptance tympanograms with increments in probe frequency agrees with other observations⁶ of notching in response to higher-frequency probes. It is generally agreed that such complex shapes are due to the

complicated interactions of the resonances of the middle ear with the higher probes. Given, however, that unified normative data on aural acoustic immittance have not yet been established, even in response to standard low-frequency probe stimuli, it is noteworthy that the immittance values obtained here, for both standard and multifrequency probe tones, are consistent with those published in several recent reviews of tympanometry.^{13,14} In addition, it is well recognized that the commercially available instrumentation used to measure clinical immittance influences reflex rise and fall times, etc., in that the absolute temporal measures of acoustic reflex parameters are affected appreciably by the response time constant of the specific device used to perform the measurements.¹⁵ Given these difficulties and others that are related to the frequency of the eliciting stimulus and the definitions adopted concerning the point in time, with respect to reflex amplitude, that a particular parameter is measured, it is reassuring that the threshold and the onset latency and rise times measured in the subjects of this report are consistent with published values of these reflex features.¹⁵⁻¹⁷ Thus, the close association of the present data with the immittance values available in the literature supports the conclusion that the 44 normal ears were indeed normal with respect to the transmission of acoustic signals from the external ear canal into and, presumably, out of the cochlea. Together, the relatively average tympanometric and acoustic reflex findings probably rule out the likelihood that peculiar resonances, lower reflex thresholds, or frequency-specific stiffenings of the ossicular chain contributed to the reduced transmission of DPEs, within the frequency extents for which diminished DPEs were documented for about one third of normally hearing ears (this Supplement, p 3).

Traditionally, the various subclasses of OAEs

have been reported on separately. However, because it is generally recognized that OAEs are interrelated, it was of interest to determine if DPE properties were influenced by the presence of other emission types within the same ears. Moreover, measures of other OAEs served to supplement the more traditionally derived information concerning the properties of middle ear conduction and also provided added details about the generation and conduction of signals within the cochlea. The detailed survey of SOEs in the ears of the 44 normally hearing subjects revealed that overall, the descriptive characteristics of SOEs in the normally hearing individuals of the present study were in general agreement with the data reported for human subjects by other investigators.¹⁸⁻²⁰ It is probable that the use of a custom-built microphone/equalizer system, which was specially developed for measuring human emissions, accounted for the slightly higher proportion of subjects exhibiting SOEs, along with the somewhat lower amplitudes, on average, of the SOEs reported here. However, whereas almost half of the ears demonstrated SOEs, no association between the presence of SOEs and the major DPE attributes was uncovered. It is important to note, though, as revealed by the data displayed in Fig 10 for one individual's two spontaneously emitting ears, that there does seem to be a systematic difference in I/O functions around SOE regions.

In contrast to the observation that SOEs were detected in only about half of the ears, all 44 ears exhibited SFEs. Similar to the statement made above concerning the normalcy of SOEs in the present population, the descriptive features of SFEs were also in general agreement with other data reported for humans. For example, to date, Zwicker and Schloth²¹ have probably reported the most detailed descriptions of these emissions, and their findings concerning the frequency distance of SFE peaks agree reasonably well with the frequency spacing reported here. Again, the difference in SFE incidences between the two studies, 100% (present subjects) versus 70%,²¹ is most likely due to technical disparities between the two measuring systems.

With respect to the present study, detailed analyses of the relationship between the presence of SFEs and the detection "thresholds" and magnitudes of DPEs showed that for the two lowest I/O test frequencies at 1 and 2 kHz, the greater the number of SFEs in a given ear, the larger the amplitudes of the acoustic distortion products. Further, DPE "thresholds" at 1 kHz were significantly lower for ears demonstrating increased numbers of SFEs. When ears exhibiting the frequency-specific reductions in DPE amplitudes were specifically examined, several examples were identified in which either SOEs or SFEs were present at reasonably normal amplitudes within the identical frequency range in which the diminished DPEs were generated. It is not surpris-

ing that only a few examples were noted in which other OAEs coexisted along with reduced DPEs, given the limited frequency ranges associated with the anomalous DPEs and the low probability that the arbitrary SOEs or SFEs would also occur within the identical frequency extent. In general, then, the findings relating DPE attributes to those of fixed-place emissions in the form of SOEs and SFEs suggest that the generation processes of the cochlea and the cochlear and/or middle ear conduction mechanisms were probably not responsible for the deficits in DPE generation noted for some ears.

A number of previous investigators have studied the influence of fixed-place emissions on acoustic distortion products.^{3,4,22-26} However, the experimental design that the majority of these studies was based on involved the deliberate examination of DPEs that occurred at the same precise frequencies as the fixed-place emissions. Consequently, the present study demonstrates a more general influence of place-fixed OAEs in the form of SFEs, regardless of their exact frequency values, that significantly influenced the "thresholds" and/or magnitudes of DPEs in the low-frequency range of 1 to 2 kHz, a frequency extent in which many SFEs and SOEs are preferentially located. These observations suggest that the cochlea's innate amplifier can modify biomechanical activity over a reasonable length of the basilar membrane that represents up to a half-octave to one-octave region, ie, at least over several millimeters. The frequency range of the SFE enhancement effect on DPEs is clearly greater than the approximately 100-Hz (ie, ± 50 Hz) extent over which SOEs influence DPE amplitudes as demonstrated by Wier et al.⁴

With use of several tests of the conduction properties of the middle ear and cochlea, it appears that in general, the ability of the ears studied here to transmit OAEs did not make a significant contribution to the form of DPEs. Although unlikely, it is possible that DPEs are not as influenced as are the other emission types by factors that restrict the conduction properties of the cochlea and middle ear. It is also conceivable that individual differences in the contribution that the cochlear efferent system makes to emission magnitude may account for the variability observed in DPE amplitudes. However, basic studies in both animals^{27,28} and humans²⁹ have shown that in general, the influence that cochlear efferents exert on OAE magnitude amounts to only a few decibels.

One factor that remains to be studied is the possibility that for the ears showing diminished DPEs over the low- to middle-frequency region, perhaps neither the standard f_2/f_1 ratio of 1.21 nor the equal-level paradigm in which L_1 equals L_2 was ideal for generating the most optimal DPEs. This proposition is supported by the wide range in amplitudes ob-

served by Harris et al² in their systematic study of the influence of the f₂/f₁ ratio on DPE magnitude. Finally, it is always possible that the clinical tests of middle ear function used here to assess the conduction of the ear were too insensitive to detect subtle

variations in the mobility of the ear over limited frequency extents. It remains for future studies to distinguish the major factors that contribute to the generation of acoustic distortion products in normally hearing ears.

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REFERENCES

1. Kemp DT, Bray P, Alexander L, Brown AM. Acoustic emission cochleography — practical aspects. *Scand Audiol [Suppl]* 1986(suppl 25):71-95.
2. Harris FP, Lonsbury-Martin BL, Stagner BB, Coats AC, Martin GK. Acoustic distortion products in humans: systematic changes in amplitude as a function of f₂/f₁ ratio. *J Acoust Soc Am* 1989;85:220-9.
3. Kemp DT. Otoacoustic emissions, travelling waves and cochlear mechanics. *Hear Res* 1986;22:95-104.
4. Wier CC, Pasanen EG, McFadden D. Partial dissociation of spontaneous otoacoustic emissions and distortion products during aspirin use in humans. *J Acoust Soc Am* 1988;84:230-7.
5. Liden G, Harford E, Hallen O. Tympanometry for the diagnosis of ossicular disruption. *Arch Otolaryngol* 1974;99:23-9.
6. Margolis RH, Van Camp KJ, Wilson RH, Creten WL. Multifrequency tympanometry in normal ears. *Audiology* 1985;24:44-53.
7. Strickland E, Burns EM, Tubis A. Incidence of spontaneous otoacoustic emissions in children and infants. *J Acoust Soc Am* 1985;78:931-5.
8. Kemp DT. Physiologically active cochlear micromechanics — one source of tinnitus. In: Evered D, Lawrenson G, eds. *Tinnitus*. CIBA Foundation symposium. London, England: Pitman, 1981:54-81.
9. Wilson JP, Sutton GJ. Acoustic correlates of tonal tinnitus. In: Evered D, Lawrenson G, eds. *Tinnitus*. CIBA Foundation symposium. London, England: Pitman, 1981:82-107.
10. Schloth E. Akustische Aussendungen des menschlichen Ohres (oto-akustische Emissionen) [Dissertation]. Munich, Federal Republic of Germany: Technical University, 1982.
11. Schloth E, Zwicker E. Mechanical and acoustical influences on spontaneous oto-acoustic emissions. *Hear Res* 1983;11:285-93.
12. Bray P, Kemp DT. An advanced cochlear echo technique suitable for infant screening. *Br J Audiol* 1987;21:191-204.
13. Hall JW. Contemporary tympanometry. *Semin Hear* 1987;8:319-38.
14. American Speech and Hearing Association Working Group on Aural Acoustic-Immittance Measurements, Committee on Audiologic Evaluation. Tutorial: Tympanometry. *J Speech Hear Disord* 1988;53:354-77.
15. Jerger JF, Oliver TA, Stach B. Problems in the clinical measurement of acoustic reflex latency. *Scand Audiol* 1986;15:31-40.
16. Jerger JF, Hayes D. Latency of the acoustic reflex in eighth-nerve tumor. *Arch Otolaryngol* 1983;109:1-5.
17. Hodges A, Ruth RA. Subject related factors influencing the acoustic reflex. *Semin Hear* 1987;8:339-58.
18. Zurek PM. Spontaneous narrowband acoustic signals emitted by human ears. *J Acoust Soc Am* 1981;62:514-23.
19. Wier CC, Norton SJ, Kincaid GE. Spontaneous narrowband oto-acoustic signals emitted by human ears: a replication. *J Acoust Soc Am* 1984;76:1248-50.
20. Dallmayr C. Stationäre und dynamische Eigenschaften sponyner und simultan evozierter otoakustischer Emissionen [Dissertation]. Munich, Federal Republic of Germany: Technical University, 1986.
21. Zwicker E, Schloth E. Interrelation of different otoacoustic emissions. *J Acoust Soc Am* 1984;75:1148-54.
22. Kemp DT. Evidence of mechanical nonlinearity and frequency selective wave amplification in the cochlea. *Arch Otolaryngol* 1979;224:37-45.
23. Wilson JP. The combination tone, 2f₁ – f₂, in psychophysics and ear-canal recording. In: van den Brink G, Bilsen FA, eds. *Psychophysical, physiological, and behavioral studies in hearing*. Delft, the Netherlands: Delft University Press, 1980:43-52.
24. Wit HP, Langevoort JC, Ritsma RJ. Frequency spectra of cochlear acoustic emissions (Kemp-echoes). *J Acoust Soc Am* 1981;70:437-45.
25. Kemp DT, Brown AM. An integrated view of cochlear mechanical nonlinearities observable from the ear canal. In: de Boer E, Viergever MA, eds. *Mechanics of hearing*. The Hague, the Netherlands: Martinus Nijhoff, 1983:75-82.
26. Furst M, Rabinowitz WM, Zurek PM. Ear canal acoustic distortion at 2f₁ – f₂ from human ears: relation to other emissions and perceived combination tones. *J Acoust Soc Am* 1988;84:215-21.
27. Mountain D. Changes in endolymphatic potential and crossed olivocochlear bundle stimulation alter cochlear mechanics. *Science* 1980;210:71-2.
28. Siegel JH, Kim DO. Efferent neural control of cochlear mechanics? Olivocochlear bundle stimulation affects cochlear biomechanical nonlinearity. *Hear Res* 1982;6:171-82.
29. Mott JB, Norton SJ, Neeley ST, Warr WB. Changes in spontaneous otoacoustic emissions produced by acoustic stimulation of the contralateral ear. *Hear Res* 1989;38:229-42.

DISTORTION PRODUCT EMISSIONS IN HUMANS III. INFLUENCE OF SENSORINEURAL HEARING LOSS

GLEN K. MARTIN, PhD

LAURIE A. OHLMS, MD
FRANCES P. HARRIS, PhD

DANIEL J. FRANKLIN, MD
BRENDA L. LONSBURY-MARTIN, PhD

HOUSTON, TEXAS

The realization that otoacoustic emissions are sensitive to cochlear disorders has resulted in the speculation that they may have considerable clinical potential as objective measures of hearing. To assess the clinical utility of one type of emission, the distortion product emission (DPE), a study was undertaken in individuals with hearing impairments representing a number of common otologic disorders. The results of this investigation provided evidence that tests of DPEs promise to satisfy a number of requirements important to clinical testing, including objectivity of measurement procedures, test-retest reliability, simple subject preparation, readily available instrumentation, and relatively brief examination periods. The fine resolution of DPEs within the stimulus frequency and level domains also permits an accurate confirmation of the pattern of hearing loss. For example, tests of DPEs detected a 20-dB hearing level impairment at a single frequency in an ear exhibiting early signs of noise-induced hearing loss, and a 10-dB improvement in sensitivity following ingestion of the hyperosmotic agent glycerol in an ear displaying a mild to moderate hearing loss due to Meniere's disease. Finally, the application of DPEs to the objective testing of otologic disorders suggests that the ability of these responses to assess the sensory component of a sensorineural disorder may contribute to the eventual understanding of the complicated pathogenesis of many cochlear diseases. When all the positive features of DPE testing are realized, the potential contribution that these measures can make in a clinical setting becomes apparent.

KEY WORDS — acoustic neuroma, distortion product emissions, hereditary hearing loss, Meniere's disease, noise-induced hearing loss, presbycusis, sudden sensorineural hearing loss.

INTRODUCTION

Otoacoustic emissions (OAEs) represent one of the most exciting recent developments in hearing research. During the immediate period following Kemp's¹ discovery of OAEs, a great deal of experimental work was aimed at defining the fundamental response properties of emissions.²⁻¹² In conjunction with the basic investigations of OAE processes, a significant number of studies were directed at clarifying the relationships among the different classes of emissions.^{10,13-15} Recently, however, investigators have begun to address issues concerning the relation of OAEs to the clinical measures of hearing.¹⁶⁻¹⁸

It is well accepted that OAEs reflect the biomechanical processing that underlies the nonlinear operations responsible for the cochlea's high sensitivity, sharp tuning, and wide dynamic range. Consequently, it seems reasonable to propose that OAEs would be useful in identifying initial disturbances in these functional properties. In fact, in his introduction of OAEs to the field, Kemp¹ noted that emissions were not present in cochlear deafness. From basic studies, it has also been established that cochlear micromechanics, as measured by OAEs, are affected by damage to the outer hair cells.¹⁹⁻²³ Because OAEs can be measured objectively and noninvasively from the external ear canal, because they operate only at low levels of stimulation, and because they preferentially evaluate the micromechanical activity of outer hair cells, a number of investigators have proposed that emissions might be

clinically useful as a diagnostic tool in identifying sensorineural hearing disorders.^{12,16,24}

One type of OAE, termed the distortion product emission (DPE), is elicited by the simultaneous application of two tones to the ear canal. These emissions arise from the nonlinear mechanical characteristics of the cochlea at a specific place having a precise mathematic relation to the frequencies of the two eliciting primary tones at f_1 and f_2 . In contrast to the other OAEs, this frequency-selective property of DPEs suggests that they will make useful monitors of localized cochlear function at any predetermined frequency.^{16,25} However, these are theoretic expectations, and little systematic information exists describing changes in DPE properties between or within specific categories of hearing loss.

Results from initial studies in normally hearing individuals (this Supplement, p 3) established the parametric features of DPEs in a population of normal ears. The present approach was designed to assess the clinical usefulness of DPE testing by comparing the response parameters of emissions in ears with known hearing loss to those measured previously in healthy ears. This goal was accomplished by testing patients representing a number of common inner ear diseases and noting the ability of DPEs to distinguish between normal and abnormal cochlear function.

METHODS

Subjects. To illustrate the practical application of

DPE testing in a clinical setting, representative cases were chosen from our ongoing collection of patient records. The types of hearing impairment selected for illustration represent disorders that are commonly encountered in clinical practice and for the most part are known to involve lesions that directly affect the sensorineural elements of the cochlea. Patients with various degrees of progressive hearing loss caused by noise ($n = 15$ ears), presbycusis ($n = 22$ ears), Meniere's disease ($n = 42$ ears), sudden sensorineural hearing loss ($n = 4$ ears), acoustic neuroma ($n = 4$ ears), and hereditary factors ($n = 16$ ears) were selected for study from the clinical practices of our colleagues subspecializing in otology or neurotology. All patients underwent routine otologic testing and audiometric examinations of hearing, speech, and middle ear function during their regular clinical workups. In the examples presented below, every patient demonstrated normal middle ear function as measured with routine clinical evaluations of aural acoustic immittance including tympanometric and acoustic reflex testing.

Distortion Product Otoacoustic Emission Testing. The stimulus generation and response detection equipment was identical to that described (this Supplement, p 3). Basically, a microcomputer controlled auxiliary instruments that generated and appropriately attenuated the two primary tones at f_1 and f_2 to produce equilevel ($L_1 = L_2$) stimuli, amplified the acoustic responses in the ear canal, and processed this signal into its basic frequency components. The measures of biomechanical distortion at the $2f_1 - f_2$ frequency that were acquired routinely included the DPE "audiogram," describing the frequency response of the ear from 1 to 8 kHz in closely spaced 100-Hz intervals. In addition, response-growth or input-output (I/O) functions, testing the dynamic range of DPEs in fine-grain steps of 5 dB at 11 separate frequencies located at quarter-octave intervals over the identical frequency range, were also obtained. The average "audiogram" and I/O functions determined previously from normally hearing ears (this Supplement, p 3) formed the basis against which DPEs from individual hearing-impaired ears were compared.

Several changes in the procedures described earlier (this Supplement, p 3) were introduced into the clinical collection protocols. First, four instead of eight frequency spectra were averaged to determine the final amplitudes of DPEs and related noise floors. This modified procedure resulted in identical DPE amplitudes, but shortened the data acquisition phase of the protocol. Second, noise floor measurements were made 50 Hz above the frequency of the $2f_1 - f_2$ DPE, rather than 20 Hz below. This strategy lowered detection "thresholds," especially for low-frequency emissions, because noise floors above the DPE were less influenced by subject-generated sounds such as respiratory, circulatory, and move-

ment-related noises. Finally, data collection time was reduced by approximately one third by deactivating the automatic ranging feature of the dynamic signal analyzer and setting response dynamic range by software and use of preselected ranges based upon previous experience (this Supplement, p 3). Consequently, the time interval required to perform an entire DPE examination on a given individual, including the evaluation of DPE "audiograms" and I/O functions in both ears, was on average 45 minutes.

It is also important to emphasize that the representation of the cochlear generation site for the $2f_1 - f_2$ DPE is approximated by the frequency equivalent to the geometric mean of the f_1 and f_2 stimuli.^{11,23} Thus, the DPE amplitudes presented below are plotted with respect to the geometric mean of the primary-evoking tones.

RESULTS

The overall finding from the detailed examination of hearing-impaired ears was that factors causing sensorineural hearing loss were associated with a concomitant reduction in OAE activity as measured with DPEs. These decrements were readily identified by comparing DPEs in ears with demonstrated sensorineural hearing losses to DPEs previously acquired from 44 normal ears (this Supplement, p 3).

In the process of comparing DPEs between hearing-impaired and normal ears, a number of key issues emerged as critical to the clinical application of these response measures. For example, for them to become a useful test of hearing function, it is important to establish if DPEs 1) are capable of testing a discrete, frequency-specific area of the cochlea, 2) can be deliberately directed so that any specific frequency region can be tested, 3) can detect mild hearing losses, 4) are sensitive to dynamic changes in cochlear disease conditions that might occur, for example, in the early stages of Meniere's disease or sudden sensorineural hearing loss, 5) can monitor progressive impairment as it is expressed, for example, in hereditary deafness, 6) can be related systematically to the magnitude of the hearing loss, and 7) can isolate the sensory component of a sensorineural disorder. In addition, we also need to know some indication of test-retest reliability and the potential of DPEs for screening hearing in difficult-to-test patients. The detailed findings presented below are organized to illuminate many of the above issues crucial to the development of DPEs as a clinical test.

Frequency Specificity. Clear illustrations of the frequency specificity of DPE testing are provided by instances of hearing loss caused by exposure to loud sounds, in which the boundary between normal and abnormal hearing is usually well demar-

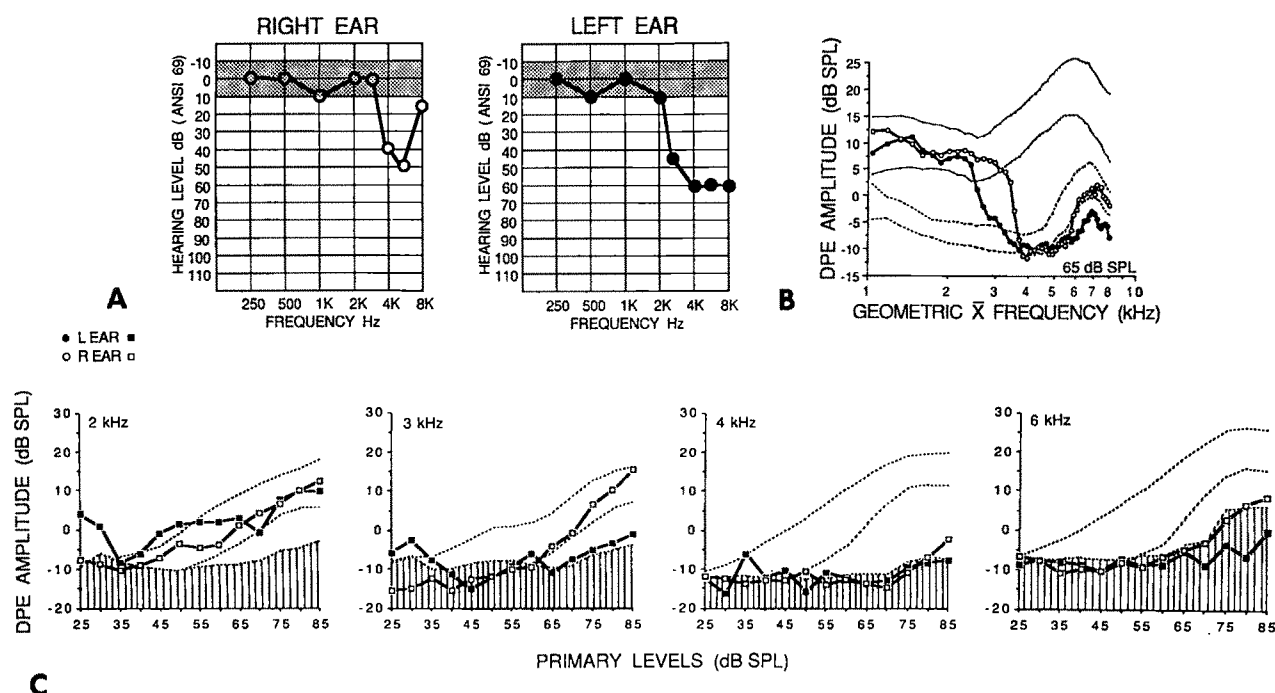


Fig 1. (Patient 1) A) Advanced noise-induced hearing loss indicated by pure-tone thresholds. Note deep 50-dB notch around 4 to 6 kHz in right ear and precipitous drop in thresholds for frequencies above 2 kHz in left ear. B) Frequency-specific "threshold" shifts were traced accurately by corresponding distortion product emission (DPE) "audiograms" that plot DPE amplitudes in response to 75-dB sound pressure level primaries as function of geometric mean of f_1 and f_2 tones. C) Input-output functions plot DPE magnitude as function of primary-tone levels for several selected frequencies. Note that at 2 kHz, both ears generated normal-like DPE activity, whereas at 3 kHz, although DPEs in right ear (open squares) were reasonably normal, left ear DPEs (solid squares) were reduced essentially to noise floor levels. At 4 and 6 kHz, where behavioral hearing exhibited bilateral 40- to 60-dB loss, no DPE activity was evident. In these and subsequent DPE "audiograms," variability of emission amplitude (± 1 SD) in normally hearing ears (this Supplement, p 3) is represented by fine dotted lines at top of each plot. Similar variability of related noise floors is indicated below by dotted-line curves along bottom of each plot. In these and subsequent DPE input-output functions, dotted lines above represent ± 1 -SD range of normal DPE amplitudes, whereas vertical stripes below indicate ± 1 -SD extent of corresponding noise floor levels.

cated. To illustrate frequency specificity in terms of distinguishing between a region of normal low-frequency hearing and one exhibiting a high-frequency hearing loss, Fig 1 depicts an example of DPEs from a reasonably advanced case of noise-induced hearing loss. For patient 1, a 28-year-old man, the bilateral, moderate, high-frequency deficit reflected in the routine audiograms at the top left resulted from the regular use of recreational firearms. Because of the protective head-shadow effect, the left ear (solid circles) in this right-handed shooter was more severely affected. The distortion product "audiograms" in Fig 1B traced the asymmetric pattern of the behavioral deficit by revealing a different frequency point, for each ear, at which the abrupt decrease in DPE amplitudes occurred. Specifically, for the better-hearing right ear (open circles), DPE amplitudes were normal until around 3 kHz, where they abruptly decreased in magnitude to noise floor levels. For this ear, the behavioral audiogram improved between 6 and 8 kHz and the DPEs also increased above this particular individual's noise floor (not plotted) over the same frequency range. In contrast, DPE amplitudes recorded from the poorer-hearing left ear (solid circles) abruptly fell to noise floor levels at about 2.5 kHz and remained depressed.

The representative DPE I/O functions shown below also reflected the asymmetric pattern of hearing loss. Close inspection of these curves indicates that in regions in which behavioral thresholds were normal, ie, around 2 kHz (far left), the amplitude functions for each ear were reasonably similar and within normal limits. However, around 3 kHz, a point at which behavioral thresholds for the right ear were still normal and those for the left ear were about 45 dB HL, the DPE I/O function for the right ear (open squares) showed only a slight shift in detection "threshold," whereas that for the left ear (solid squares) exhibited a significant "threshold" shift. Additionally, the amplitudes of the DPEs for the left ear never increased above the noise floor beyond 3 kHz. At 4 and 6 kHz, where both ears demonstrated behavioral threshold shifts of 50 to 60 dB, the DPE amplitudes remained at noise floor levels. Thus, such detailed analyses in the frequency extent indicated quite accurately the frequencies at which a particular cochlea was mechanically inactive. These results support the useful application of DPEs for tracking the distinct boundary between normal hearing and hearing impairment caused by exposure to loud sound.

Sensitivity. Although the example presented

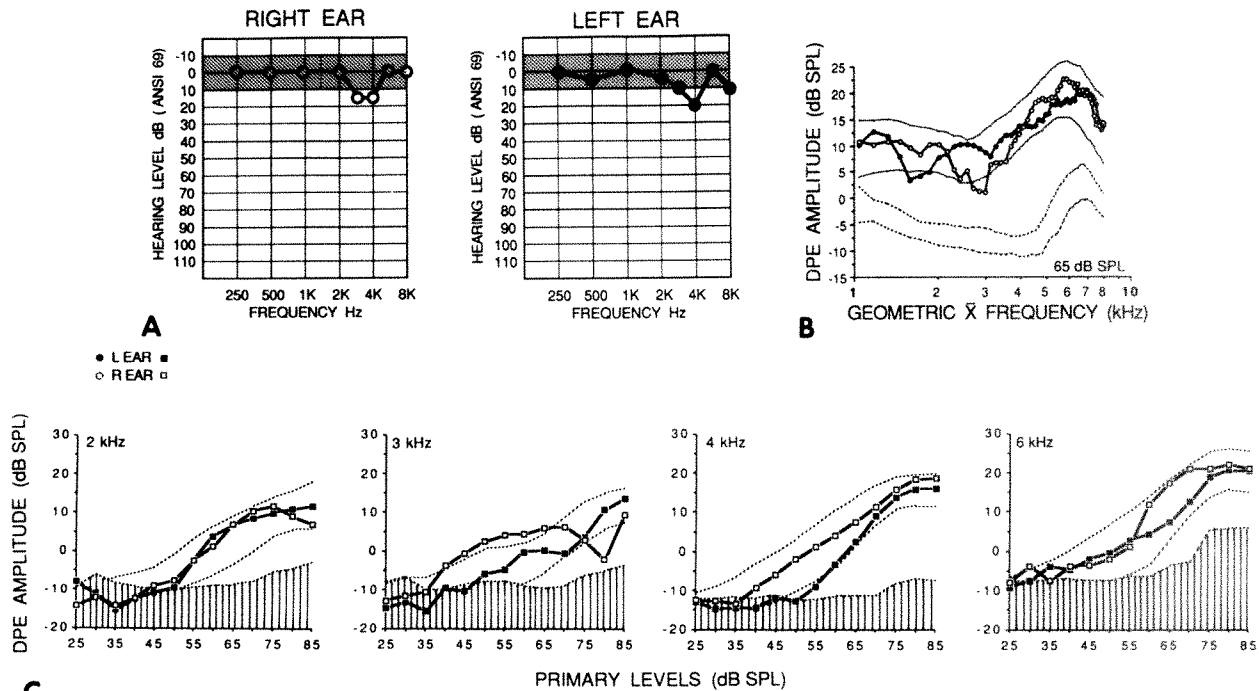


Fig 2. (Patient 2) A) Audiogram showing near-normal hearing except for small bilateral notch at 3 to 4 kHz that resulted from exposure to loud noise. B) Distortion product emission (DPE) "audiograms" elicited by 65-dB sound pressure level primaries did not reliably detect behavioral threshold shifts. C) Input-output functions indicated that 20-dB hearing loss at 4 kHz in left ear (solid squares) was associated with slight "threshold" shift and steeper slope for DPE activity in that ear.

above supports the notion that DPE testing can adequately measure the frequency pattern of remaining hearing, the DPEs shown in Fig 2 illustrate the proficiency of this class of emission in detecting a very mild hearing loss of about 20 dB hearing level (HL) in a patient demonstrating the beginning stages of a bilateral noise-induced hearing loss. In this instance, patient 2, a 26-year-old woman, had served in the military for 3 years as a member of a flight ground crew. Note that the DPE "audiogram" in response to even the lowest primary-tone levels at 65 dB SPL (Fig 2B) did not detect a convincing region of reduced emission activity for either ear in this subject. The DPE I/O curves shown in Fig 2C displayed fairly normal DPEs except around 4 kHz, where the behavioral threshold shift of 20 dB HL in the left ear (solid circles) was associated with a DPE I/O function (solid squares) exhibiting a slight "threshold" shift and a somewhat steeper slope than noted for the less impaired contralateral ear. Consequently, although DPEs appeared not to detect the fairly focused 15-dB HL hearing loss displayed by the right ear (open circles), they did satisfactorily uncover the 20-dB HL hearing deficit in the left ear caused by noise exposure, a harmful agent known to be specific to the outer hair cell system in the early stages of hearing loss. A discrete 10-dB notch was also noted at high primary-tone levels in the 3-kHz I/O curve of the right ear (open squares). The dip in this function was associated with several low-frequency SOEs. It is noteworthy that a similar influence of SOEs on the form of DPE I/O functions has also been identi-

fied in normal ears (this Supplement, p 27).

Another example of DPE sensitivity to a restricted cochlear loss is provided in Fig 3 by a case of presbycusis. For patient 3, a 60-year-old woman, the results of routine pure-tone audiometry (Fig 3A) indicated the beginning of a very mild, high-frequency hearing loss. The high-frequency dip in the DPE "audiogram" in Fig 3B supports the contention that patient 3's presbycusis was associated primarily with a loss of outer hair cells at this stage of the disease process. It is noteworthy that although the behavioral thresholds between 1 and 2 kHz remained reasonably normal, DPE I/O activity, for the lowest test frequencies, detected mildly shifted DPE "thresholds."

The examples presented above in Figs 2 and 3 represent demonstrations in which DPEs were capable of detecting small permanent hearing losses. Subsequent examples illustrate the sensitivity of the DPE technique to dynamic changes in hearing threshold. In the first case, shown in Fig 4, patient 4, a 48-year-old woman, was diagnosed as suffering from Meniere's disease on the basis of the presence of the classic trilogy of associated symptoms: tinnitus, fluctuating hearing loss, and episodic vertigo. This characteristic syndrome had been present for 3 years in the left ear (below) and for 3 months in the right ear (above). To further substantiate this diagnosis, the hyperosmotic agent glycerol was administered orally (1.2 g/kg) immediately following the initial measures (solid symbols) of behavioral thresholds and DPEs. Approximately 3 hours after

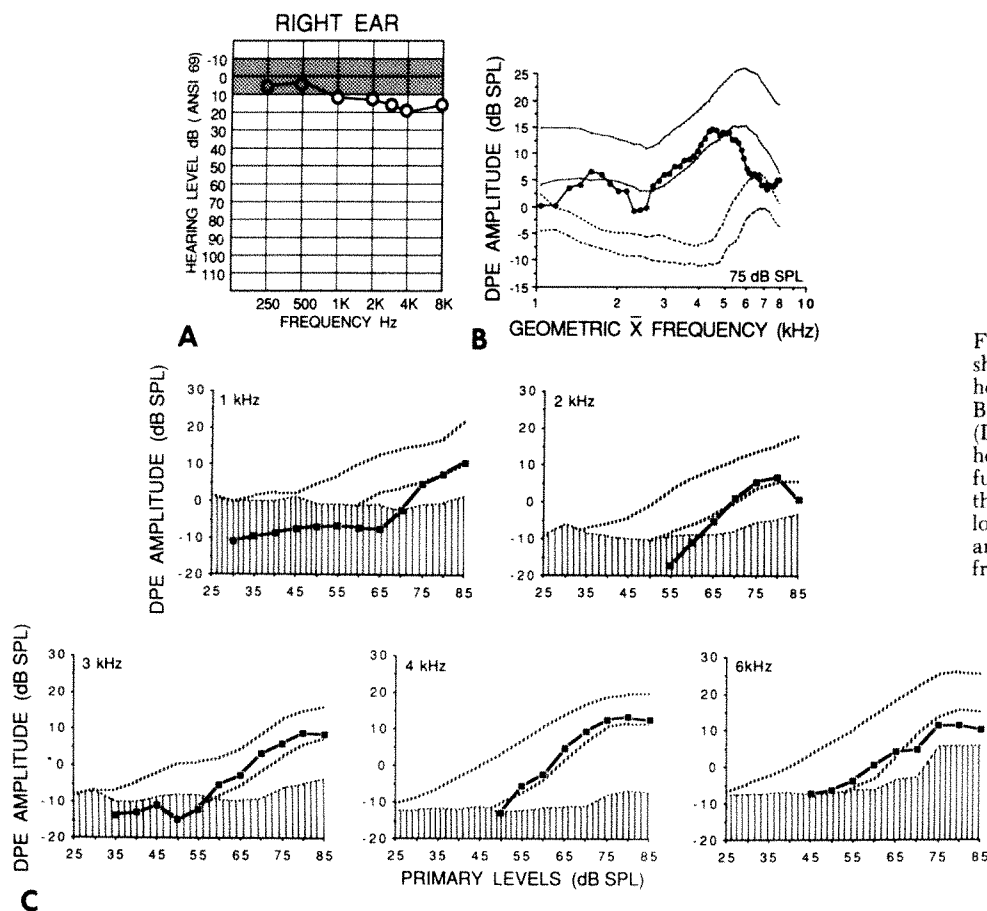


Fig 3. (Patient 3) A) Audiogram showing mild, high-frequency hearing loss associated with aging. B) Distortion product emission (DPE) "audiogram" also reflected hearing loss. C) DPE input-output functions also depicted minimal threshold shifts and reduced or low-normal amplitudes for cochlear mechanical activity over similar frequency range.

glycerol ingestion, pure-tone hearing thresholds and the amount of DPE activity were redetermined. The conventional audiogram and DPE I/O functions, illustrated in the lower portion of the figure, demonstrate that although hearing and DPE functioning in the left ear did not change appreciably in response to glycerol dosing, those measured in the right ear, displayed above, showed some minimal recovery. Specifically, following glycerol ingestion (open circles), the audiogram at the top left revealed a 5- to 10-dB improvement in hearing sensitivity between 1 and 8 kHz. Illustrated at the top right are representative DPE I/O functions for three frequencies within this same frequency range. Both DPE "thresholds" and their magnitudes, as a function of primary-tone level, also showed significant improvements. Thus, in this patient, DPEs detected the minimal but dynamic changes in hearing level.

Other examples of the capability of DPEs to follow dynamic changes in hearing are provided by cases involving sudden sensorineural hearing loss. The functional data of Fig 5 illustrate in patient 5, a 28-year-old woman, an example of a sudden hearing loss that followed an upper respiratory tract infection. The hearing levels shown at the top left indicate the results of standard pure-tone audiometric testing that was completed within a few days of the onset of hearing loss (solid circles) compared to those acquired several months later (open circles)

following a conventional regimen of treatment that included bed rest, steroids, carbogen, and stellate ganglion block. The outcome of this treatment resulted in a slight to moderate improvement in hearing, ranging from a few decibels to 40 dB, above about 2 kHz. The differences between the two successive DPE "audiograms" displayed at top right demonstrate that during this time, emission activity also improved to the extent that between about 3.5 to approximately 7 kHz, DPE amplitudes recovered to the normal range. Such improvement in cochlear function is also supported by the DPE I/O activity shown below, in that although essentially no improvement was detected around 2 (lower left) or 8 kHz (lower right), response growth, as a function of systematic increases in primary-tone levels, became relatively normal (open squares) for frequencies between these two limits. Again, changes in DPE amplitudes and "thresholds" followed reasonably accurately a short-term improvement in hearing sensitivity.

Test-Retest Reliability. Test-retest reliability is an important feature of any clinical assessment. At this time, we have not made a dedicated effort toward examining this particular property of DPE measurement over long time periods. However, to date, within-session test-retest reliability has been examined in more than 40 instances in which glycerol testing was performed in patients suspected of

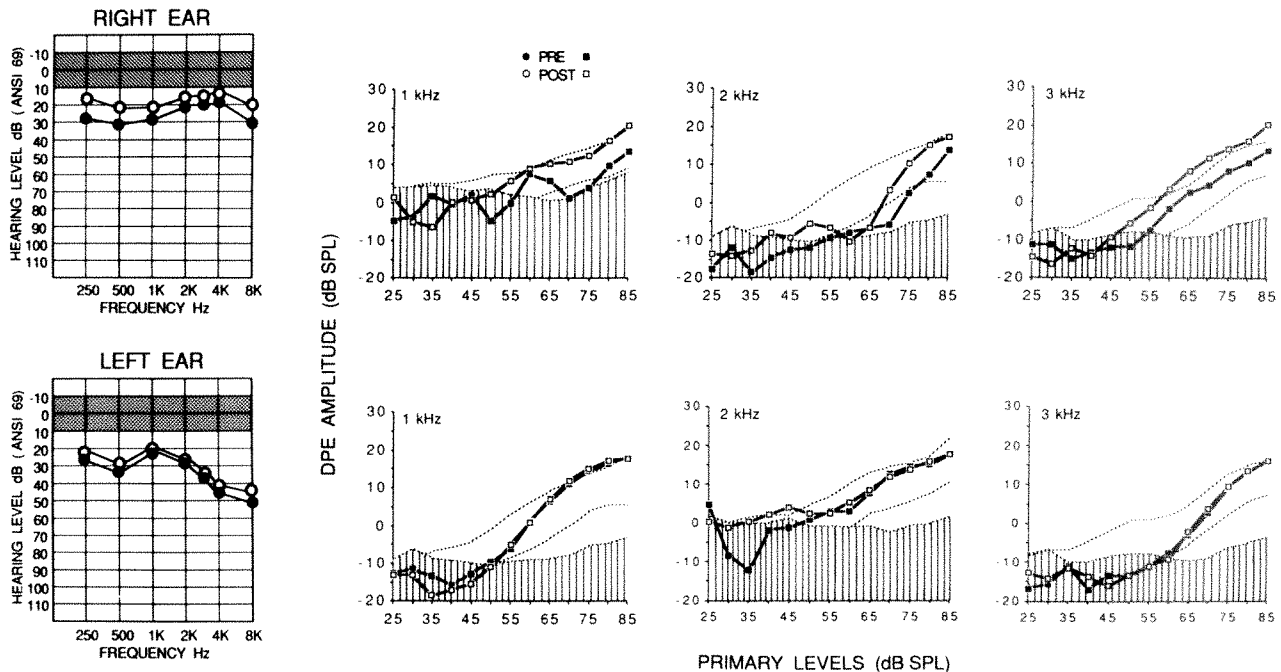


Fig 4. (Patient 4) Patient had bilateral Meniere's disease of 3 months' duration in right ear and of 3 years' duration in left ear. Functional data were collected before (solid symbols) and after (open symbols) glycerol administration, with each session separated by 3 hours. Audiometric findings indicated at left show that glycerol improved thresholds in newly diagnosed right ear by 5 to 10 dB, whereas elevated thresholds in left ear were not influenced by hyperosmotic agent. Corresponding distortion product emission (DPE) input-output functions to right illustrate concomitant improvement in DPE detection "thresholds" and amplitudes for right, but not left ear. Note excellent test-retest consistency of DPE data points for stable left ear over short 3-hour period.

having Meniere's disease. According to our standard glycerol protocol, a patient's hearing is examined initially with standard pure-tone audiometry, followed immediately by the determination of DPE magnitudes and detection "thresholds" by use of both the I/O and "audiogram" paradigms. After the DPE measures have been completed, the acoustic speculum, incorporating both the sound tube from the nearby speakers and the subminiature microphone system, is removed from the ear canal. The patient is then instructed to ingest a small glass of glycerol flavored with lemon juice. Three hours later, when the patient has returned to the test facility, hearing levels are redetermined audiometrically. Following determination of postglycerol hearing thresholds, the acoustic speculum is reinserted into the outer ear canal and DPEs are reexamined. The DPE data for the stable left ear of patient 4, with Meniere's disease, illustrated in the bottom portion of Fig 4, serve to demonstrate the excellent reliability of emission measures under such short-term conditions. Specifically, along with the lack of improvement in audiometric thresholds, close inspection of the adjacent DPE I/O curves reveals remarkably consistent amplitude values between preglycerol (solid squares) and postglycerol (open squares) DPEs, which were separated in time by more than 3 hours. These results not only confirm the excellent test-retest features of DPE measures, but they also underscore the accuracy that computer-controlled measures of objective responses can have.

Response Specificity and Diagnosis of Site of Dis-

order. On the basis of a number of fundamental studies in experimental models, it has been well established that emissions in the form of DPEs selectively measure the activity of outer hair cells. The knowledge that DPEs reflect outer hair cell activity provides a unique opportunity to separate disorders that preferentially affect these sensory cells from other types of cochlear disease. Thus, it would be expected that hearing afflictions considered to be caused primarily by damage to the outer hair cell system represent instances in which DPEs should mimic quite precisely the behavioral hearing loss pattern. This outcome was certainly the case in the examples of sound-induced hearing impairment illustrated in Figs 1 and 2.

Further, it would be expected that for ear disorders that are thought to involve many cochlear components — for example, Meniere's disease, sudden sensorineural hearing loss, or presbycusis — DPEs would not so accurately depict the audiometric profile if peripheral elements other than the outer hair cells were involved in the disease process. For example, the pathogenesis of Meniere's disease remains largely unknown despite well-established observations, over the past 60 years or more, that one of the primary changes involves hydrops of the endolymphatic space.²⁶ However, the application of electron microscopy has indicated that in some cases, damage to the unmyelinated afferent nerve fiber endings may be more pivotal to the Meniere's disease process than injury to the sensory cells.²⁷ Thus, on the basis of the extent of outer hair cell in-

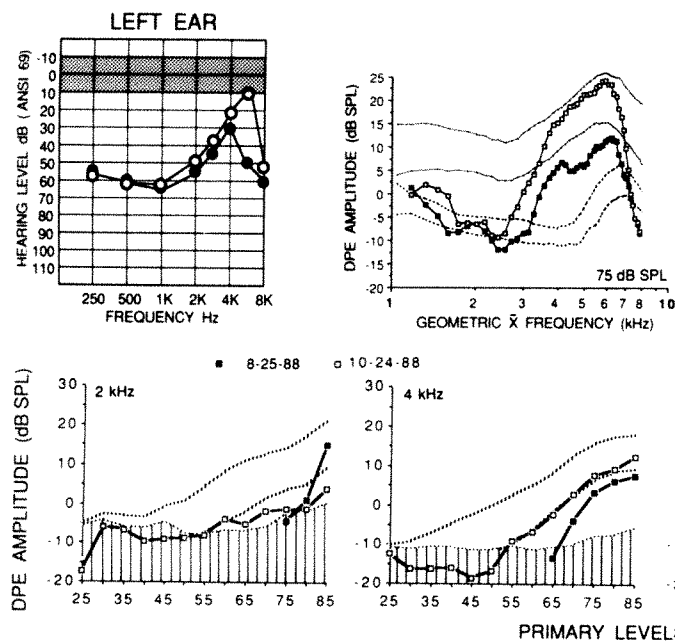


Fig 5. (Patient 5) In patient exhibiting sudden sensorineural hearing loss in left ear, note ability of distortion product emission (DPE) "audiograms" and input-output functions to track changes in hearing that occurred between initial diagnosis (solid symbols) and following conventional treatment (open symbols).

volvement, it would not be surprising to find individuals showing similar symptoms of inner ear dysfunction and patterns of hearing loss but distinct differences in their corresponding DPE measures.

The functional data shown in Fig 6 illustrate this type of incongruity in Meniere's disease. Both patient 6, a 41-year-old woman (above), and patient 7, a 51-year-old woman (below), demonstrated flat 30- to 60-dB hearing impairments associated with well-developed symptoms indicative of Meniere's disease. The lack of any DPE responses in patient 6

was consistent with her hearing loss and indicated that the disease had produced a severe sensory cell loss. In contrast, patient 7 (below), with approximately the same amount of hearing impairment, was capable of generating near-normal DPE I/O functions. These results suggest that the hydropic disease process had dramatically different effects on the survival of each patient's outer hair cells.

It can also be noted that the left ear of patient 4 (Fig 4), who had a less severe case of Meniere's disease, also demonstrated emissions that were more

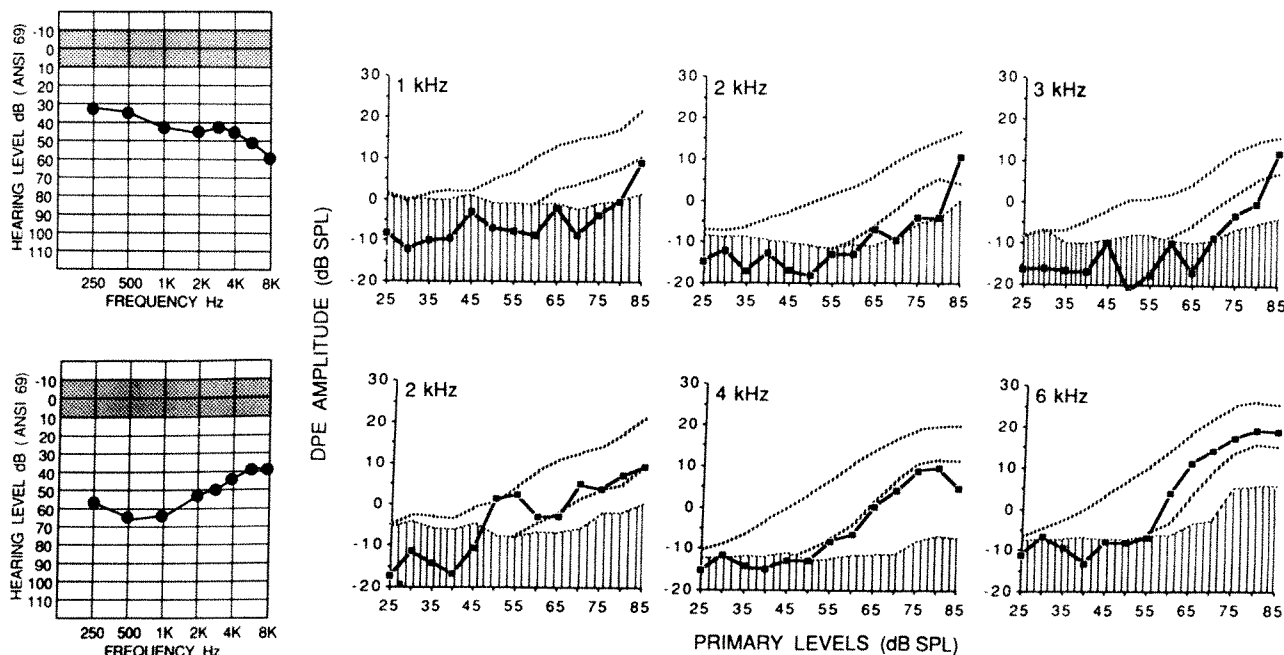


Fig 6. Comparison of distortion product emission (DPE) input-output functions of left ears of two patients with Meniere's disease. Despite similar clinical histories, patients 6 (top) and 7 (bottom) demonstrated unique DPE patterns. Patient 6 demonstrated decreased DPEs with shifted "thresholds" that were consistent with her moderately severe hearing loss. Patient 7 displayed robust DPEs that accompanied 50- to 60-dB elevations in hearing levels. These findings indicate that patient 7's hearing loss was not of outer hair cell origin, but most likely represented injury to more central cochlear structures.

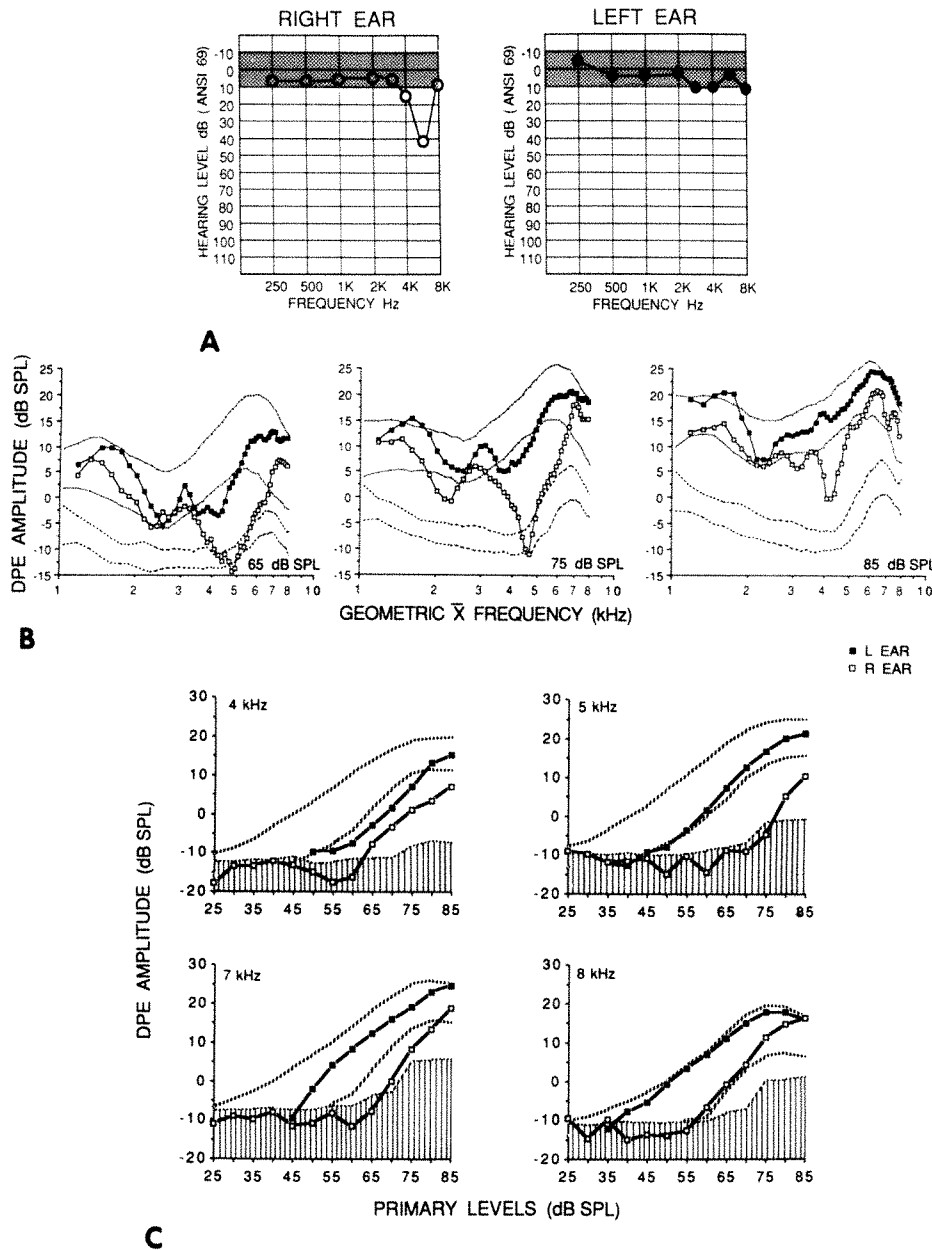


Fig 7. (Patient 8) A) Restricted hearing loss of unknown cause consisted of discrete notch at 6 kHz in routine audiogram for right ear. B) Frequency-specific threshold shift for right ear was traced accurately by corresponding distortion product emission (DPE) "audiograms" (open squares). C) Input-output plots depict hearing loss noted for right ear (open squares), whereas DPE magnitudes for left ear (solid squares) were fairly normal.

robust than would have been expected in the presence of her 20- to 50-dB hearing loss. The significance of this outcome can be appreciated by comparing these findings with those from the noise-induced hearing loss case illustrated in Fig 1. Again, a discrepancy exists between similar hearing levels in the presence of considerably different amounts of DPE activity.

From the above discussion it is clear that acoustic distortion products can be extremely useful in determining the primary site of pathologic involvement in instances in which the basis of hearing impairment is unknown. For example, the functional data illustrated in Fig 7 for patient 8, a 26-year-old man, demonstrate the presence of a unilateral hearing loss of unknown origin in the right ear. The resulting impairment was very localized, in that accord-

ing to the conventional audiogram (Fig 7A), the 15- to 40-dB hearing loss was confined to a frequency range of slightly more than one octave, ie, between 3 and 8 kHz. The DPE "audiograms" (Fig 7B) elicited by the three customary primary-tone levels (65, 75, and 85 dB SPL) clearly tracked the limits of this restricted hearing loss. The DPE I/O functions displayed in Fig 7C similarly reflected the "threshold" shifts and reductions in amplitudes for emissions measured in the impaired right ear (open squares). These findings indicate that the major source of patient 8's hearing loss was probably damaged outer hair cells and support, once again, the notion that tests of DPEs are sensitive to moderately discrete regions of hearing loss.

Another approach available for examining the specificity of DPEs is to determine the effects of dis-

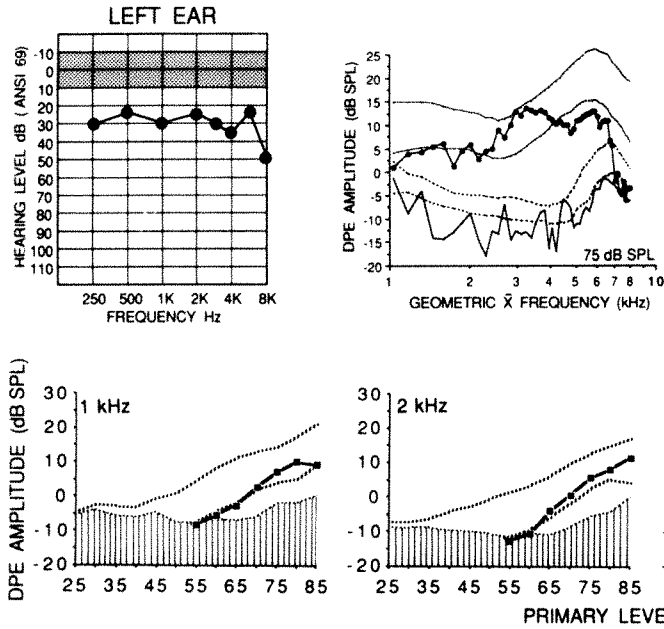


Fig 8. (Patient 9) Audiometric and distortion product emission (DPE) measures for patient with surgically confirmed 2-cm acoustic neuroma on left side. Both DPE "audiogram" and input-output functions were normal up to about 4 kHz, despite presence of approximately 30-dB elevation in hearing thresholds. Abnormal DPE activity noted on DPE "audiogram" for frequencies above 4 kHz was related to presbycusis in this 62-year-old individual.

eases that are thought to be solely retrocochlear in origin on emission generation. For example, acoustic neuromas theoretically involve eighth-nerve elements only and should not affect cochlear hair cell responses. This predicted lack of effect of an acoustic neuroma on outer hair cell activity is shown in Fig 8 for a 62-year-old woman. The routine audiograms illustrated at the top left of Fig 8 depict a relatively flat hearing loss of about 30 dB caused by a surgically confirmed 2-cm tumor. The DPE "audiogram" shown at the top right and the I/O functions displayed below support the contention that

this acoustic neuroma did not appreciably influence the generation of acoustic distortion products. However, because both the vasculature and the efferent innervation supplying the cochlea are contained within the eighth nerve, it is likely that large acoustic neuromas, through mechanical compression, will exert a deleterious influence on emissions generated by outer hair cells.

A final means of assessing DPE specificity is to examine the strength of the association between DPE properties and the magnitude of hearing loss in dis-

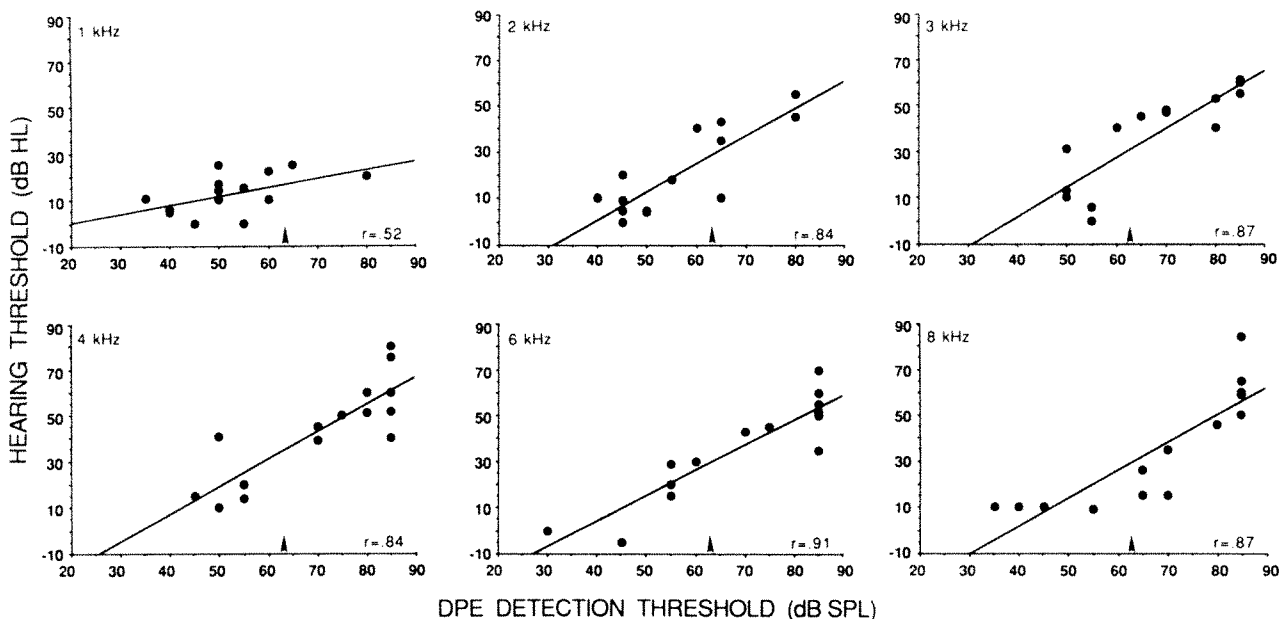


Fig 9. Relation between distortion product emission (DPE) detection "thresholds" and hearing levels in ears with noise-induced hearing loss. It is clear that for frequency regions primarily associated with sound damage, ie, especially at 3 to 4 kHz, as hearing loss increased, DPE "thresholds" also increased systematically. Arrowhead on abscissa indicates DPE detection "threshold" below which 95% of normal ears fell (this Supplement p 3). Correlational value at lower right of each plot denotes strength of relationship of hearing loss to DPE "threshold" with respect to simple straight-line fit. Data points in each plot represent single measure from each of 15 ears. In most plots, only 14 data points are evident because of overlapping values.

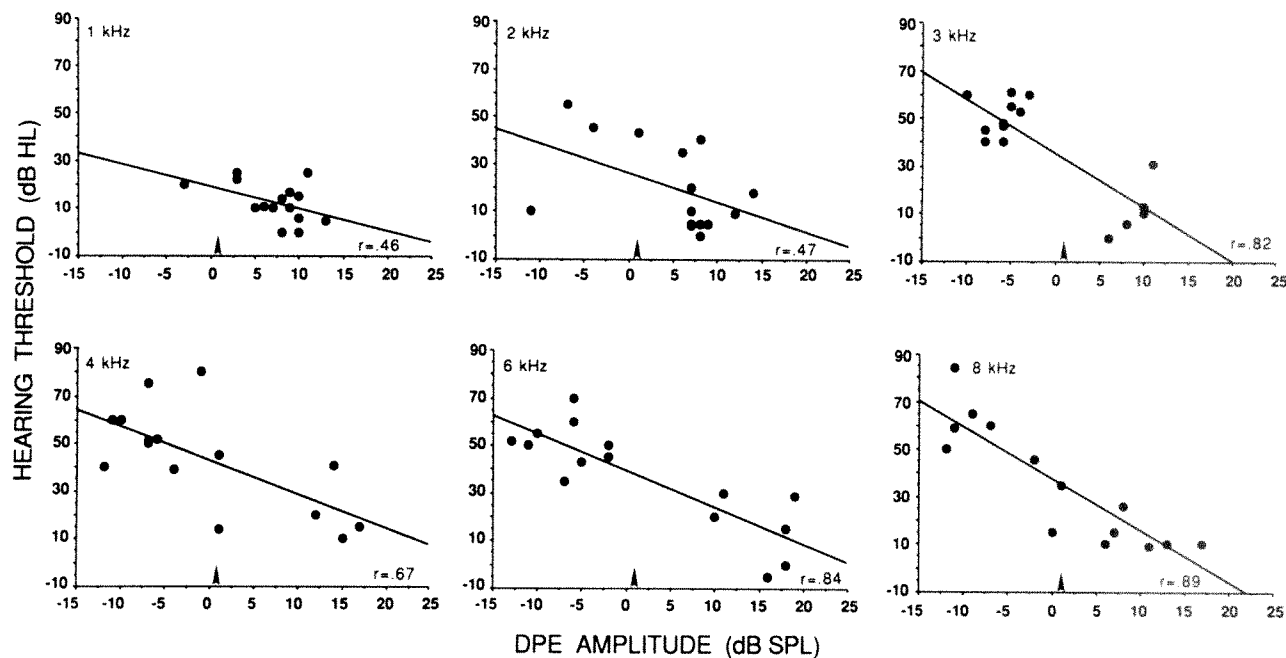


Fig 10. Relation between distortion product emission (DPE) amplitudes and hearing levels in response to 75-dB SPL primaries for ears with noise-induced hearing loss. As in Fig 9 for DPE "thresholds," moderate correlation existed between DPE amplitudes and hearing level. However, for any one level of hearing, considerable range of DPE responses was present. Arrowhead on abscissa indicates DPE amplitude above which 95% of normal ears are found.

orders in which it can be assumed that the primary pathologic changes involved the outer hair cells. In Fig 9, the amount of hearing loss versus the DPE detection "threshold" is compared, in the form of scatterplots, for emission data collected from 15 noise-damaged ears at six representative frequencies ranging from 1 to 8 kHz. The correlation coefficient, based upon a least-squares regression analysis that best fits a straight line to the data points, is shown in the lower right corner of each plot. The noise exposure data represented hearing impair-

ments ranging from discrete notches restricted to the 3- to 4-kHz region to severe high-frequency losses. Even with such various degrees and patterns of hearing loss, it is clear that at a frequency at which the majority of ears demonstrated mild to severe losses, ie, at 3 kHz (top right), a relatively strong relationship existed between DPE "thresholds" and the magnitude of hearing loss. For example, at this frequency, if the DPE "threshold" was >63 dB SPL, the accompanying hearing loss was >30 dB HL.

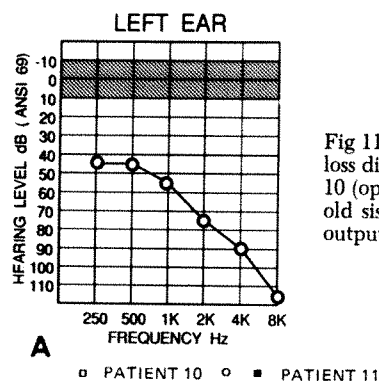
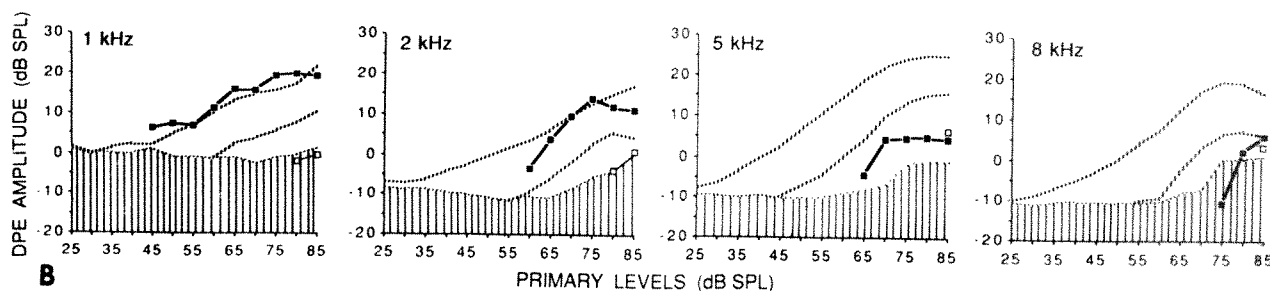


Fig 11. A) (Patient 10) Conventional audiogram of 6-year-old boy with bilateral sensorineural hearing loss diagnosed at 3 years of age. B) (Patients 10 and 11) Distortion product emissions (DPEs) of patient 10 (open squares) were nondetectable, consistent with his profound hearing loss. Patient 11, his 3-year-old sister, had been tested under open sound-field conditions with normal results. Her DPE input-output functions (solid squares) demonstrated decreased DPEs in high-frequency range.



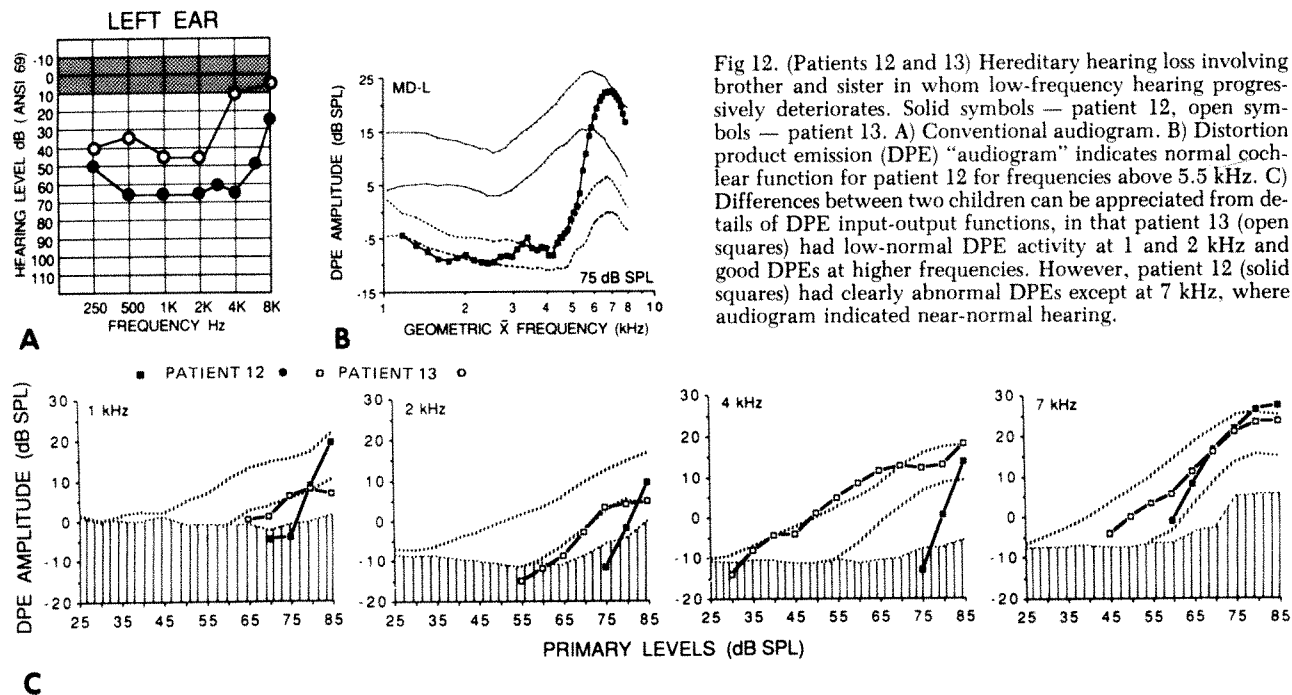


Fig 12. (Patients 12 and 13) Hereditary hearing loss involving brother and sister in whom low-frequency hearing progressively deteriorates. Solid symbols — patient 12, open symbols — patient 13. A) Conventional audiogram. B) Distortion product emission (DPE) “audiogram” indicates normal cochlear function for patient 12 for frequencies above 5.5 kHz. C) Differences between two children can be appreciated from details of DPE input-output functions, in that patient 13 (open squares) had low-normal DPE activity at 1 and 2 kHz and good DPEs at higher frequencies. However, patient 12 (solid squares) had clearly abnormal DPEs except at 7 kHz, where audiogram indicated near-normal hearing.

The scatterplots of Fig 10 illustrate similar findings for DPE magnitude in response to 75-dB SPL primaries and the amount of hearing loss measured audiometrically. Again, if a frequency range in which the majority of cases demonstrated a noise-induced threshold shift is inspected, for example, at 3 kHz, a good correlation between DPE amplitude and related hearing loss is seen. In this instance, if DPE amplitude was < 0 dB SPL, hearing threshold was typically > 30 dB HL. Thus, in frequency regions dominated by a noise-induced injury, DPE detection “thresholds” and amplitudes have a systematic relationship to behavioral hearing. These results support the contention that DPEs are testing outer hair cell function.

It is important to note that in the scatterplots of Figs 9 and 10, a small percentage of individuals with normal hearing, ie, with thresholds ≤ 20 dB HL, demonstrated either unnaturally high DPE “thresholds” or abnormally low amplitudes. Thus, in predicting behavioral hearing level from these DPE parameters, such cases represent “false-positives” in which poor “thresholds” or amplitudes would have signified poor hearing. Whether these anomalous cases represent “true” false-positives or, in fact, indicate that the DPE measures detected damage to outer hair cells that was not discovered by conventional audiometry remains to be determined.

Practical Applications of DPE Testing. Distortion product emissions testing offers some advantages in special testing situations. For example, some practical uses of objective tests of audiometry involve examining difficult-to-test patients as well as the long-term monitoring of progressive hearing disorders. An obvious example of both of these important ap-

plications would be screening for hearing loss in newborns at high risk for hearing impairment and monitoring the consequences of hereditary hearing loss in young children. Although we have not yet focused on the objective screening of newborns, several occasions have arisen to test the proficiency of DPEs in detecting hearing impairment in “high-risk” youngsters. For example, the seemingly normal hearing of younger children with older siblings who already have been diagnosed as possessing some form of hereditary hearing loss provided an opportunity to perform a test of this sort. The conventional audiogram at the top left of Fig 11 illustrates the hearing sensitivity for the left ear of patient 10, a 6-year-old boy with a bilateral hearing loss that had been diagnosed at age 3 years. The DPE I/O functions below compare his essentially nondetectable emissions (open squares) with those of his 3-year-old sister, patient 11 (solid squares), who had been tested under open sound-field conditions with normal results. It is clear from these data that although patient 11 exhibited normal-like DPE magnitudes for lower-frequency stimuli at 1 and 2 kHz, her high-frequency DPEs at 5 and 8 kHz were clearly abnormal. Thus, in this case, DPE testing identified the beginning stages of a probable high-frequency, hereditary hearing loss that went undetected by behavioral techniques.

To date, we have not deliberately monitored DPEs in any clinical case in a longitudinal manner. However, the testing of siblings of distinctly different ages with hereditary hearing loss presented an opportunity to simulate this approach. For example, the audiometric and DPE data illustrated in Fig 12 compare, for patient 12 (solid symbols), a 13-year-old girl, the current status of a sensorineu-

ral hearing loss that had been identified at age 6 years to that of her 7-year-old brother, patient 13 (open symbols), who had been found at age 4 years to have a similar impairment. The audiometric findings at the top left show that at the time of testing, patient 13's impairment was not as advanced as his older sister's disability. In agreement with this inference, the DPE I/O functions displayed below indicate that although patient 13 still had good cochlear function at test frequencies above 2 kHz, the reduced low-frequency DPE activity was approaching the levels exhibited by his older sister, implying that further degeneration of outer hair cells in this region will likely occur over the next few years.

DISCUSSION

Clinicians have long searched for a means of objectively assessing cochlear status. Findings from the representative clinical cases presented above indicate that DPEs are an objective and reproducible measure of cochlear outer hair cell function. Further, the experimental paradigms used to elicit DPEs at the $2f_1 - f_2$ frequency permit high-resolution testing in both the stimulus frequency and level domains. This fine control over stimulus parameters permits DPEs to detect small changes in cochlear status associated with a variety of hearing disorders. Additionally, although advanced hearing losses caused by exposure to noise and genetic factors tend to be comparatively stable, dysfunction associated with Meniere's disease or sudden hearing loss often remains in a dynamic state, especially during the early phase of the disease process. The capability of DPEs to detect alterations induced by ameliorating agents like glycerol or steroids provides an added dimension to this type of objective testing. Moreover, the potential for differential diagnosis, ie, the ability of DPEs to separate the sensory from the neural component of a sensorineural hearing loss, represents one of the most significant contributions of DPE testing. Thus, these measures of cochlear integrity, along with their relationship to pure-tone thresholds, may provide insight into the detailed nature of the cochlear damage caused by disease or harmful agents.

It is important to stress that the findings discussed in the present report by no means exhaust the potential applications of DPE testing in practical settings. For example, identification of the functional effects of lesions, in specific frequency regions, produced by noise exposure or ototoxic drug administration, and monitoring the progression of such abnormalities, would clearly be of benefit in industrial and hospital settings, respectively. Screening for the early effects of such agents that primarily harm the

outer hair cells would play a critical role in the prevention of probable hearing loss. Moreover, the rapid and objective audiologic assessment of receptor function afforded by DPE testing has an important part in screening populations at risk for hearing loss. It is clear that the objective screening potential afforded by DPEs could be used with high-risk neonates or even for screening hearing in newborns in general. Such testing would require significantly less time and would be more frequency-specific in determining the boundaries between normal and abnormal hearing than the currently used electrical recordings of auditory brain stem responses.

A great deal of effort has been expended by other investigators to develop the transiently evoked emissions technique into a clinical test of hearing.²⁸ However, other than some pilot data collected by Kemp et al¹⁶ in several subjects with impaired hearing, there have been no systematic attempts to develop the use of DPEs into a clinical procedure. Although it may seem that the availability of two types of emissions testing is redundant, it is highly probable that the transiently evoked emissions and DPEs evaluate different aspects of the same cochlear amplifier.¹⁶ Consequently, tests of each type of emission will most likely contribute complementary but unique information concerning the cochlear origin of a particular hearing disorder at the level of the outer hair cells. For example, it is well recognized that transiently evoked emissions detect simply the presence of a hearing loss without providing a great deal of quantitative information concerning the magnitude of the impairment or the specific frequencies involved. From the present data, it appears that the DPE features of "threshold" and magnitude may have a more systematic relationship to the corresponding amount of behavioral hearing loss. Similarly, the emission data presented above clearly demonstrate the frequency specificity of DPE activity.

Our laboratory has actively developed the instrumentation and controlling software that enable DPEs to be efficiently tested in a reasonably short time interval. In addition, we have performed a number of experiments in normally hearing human²⁵ (also this Supplement, pp 3 and 15) and animal^{23,29,30} ears to determine the optimal stimulus parameters for eliciting the $2f_1 - f_2$ emission including the f_2/f_1 ratio and the ranges over which primary-tone levels and frequencies can vary. The normative data presented by Lonsbury-Martin et al (this Supplement, pp 3 and 15), along with the positive clinical features of DPE testing detailed in the present report, make an initial contribution toward the development of DPE testing as an important part of the audiologic examination.

REFERENCES

1. Kemp DT. Stimulated acoustic emissions from within the human auditory system. *J Acoust Soc Am* 1978;64:1386-91.
2. Kemp DT. Evidence of mechanical nonlinearity and frequency selective wave amplification in the cochlea. *Arch Oto-*

rhinolaryngol 1979;224:37-45.

3. Kemp DT. Towards a model for the origin of cochlear echoes. *Hear Res* 1980;2:533-48.

4. Kemp DT. Otoacoustic emissions, travelling waves and cochlear mechanics. *Hear Res* 1986;22:95-104.

5. Kim DO. Cochlear mechanics: implications of electrophysiological and acoustical observations. *Hear Res* 1980;2:297-317.

6. Kemp DT, Chum R. Properties of the generator of stimulated acoustic emissions. *Hear Res* 1980;2:213-32.

7. Wit HP, Ritsma RJ. Evoked acoustical responses from the human ear: some experimental results. *Hear Res* 1980;2:253-61.

8. Zurek PM. Spontaneous narrowband acoustic signals emitted by human ears. *J Acoust Soc Am* 1981;62:514-23.

9. Fritze W. Registration of spontaneous cochlear emissions by means of Fourier transformation. *Arch Otorhinolaryngol* 1983;283:189-96.

10. Schloth E. Relation between spectral composition of spontaneous otoacoustic emissions and fine-structure of thresholds in quiet. *Acustica* 1983;53:250-6.

11. Brown AM, Kemp DT. Suppressibility of the $2f_1 - f_2$ stimulated acoustic emissions in gerbil and man. *Hear Res* 1984;13:29-37.

12. Probst R, Coats AC, Martin GK, Lonsbury-Martin BL. Spontaneous, click-, and toneburst-evoked otoacoustic emissions from normal ears. *Hear Res* 1986;21:261-75.

13. Burns EM, Strickland EA, Tubis A, Jones K. Interactions among spontaneous otoacoustic emissions. I. Distortion products and linked emissions. *Hear Res* 1984;6:271-8.

14. Long GR. The microstructure of quiet and masked thresholds. *Hear Res* 1984;15:73-87.

15. Zwicker E, Schloth E. Interrelation of different otoacoustic emissions. *J Acoust Soc Am* 1984;75:1148-54.

16. Kemp DT, Bray P, Alexander L, Brown AM. Acoustic emission cochleography — practical aspects. *Scand Audiol [Suppl]* 1986(suppl 15):71-96.

17. Probst R, Lonsbury-Martin BL, Martin GK, Coats AC. Otoacoustic emissions in ears with hearing loss. *Am J Otolaryngol* 1987;8:73-81.

18. Bonfils P, Uziel A, Pujol R. Evoked oto-acoustic emissions

from adults and infants: clinical applications. *Acta Otolaryngol (Stockh)* 1988;105:445-9.

19. Kemp DT. Cochlear echoes: implications for noise-induced hearing loss. In: Hamernik RP, Henderson D, Salvi R, eds. *New perspectives on noise-induced hearing loss*. New York, NY: Raven Press, 1982:89-207.

20. Siegel JH, Kim DO. Efferent neural control of cochlear mechanics? Olivocochlear bundle stimulation affects cochlear biomechanical nonlinearity. *Hear Res* 1982;6:171-82.

21. Clark WW, Kim DO, Zurek PM, Bohne BA. Spontaneous otoacoustic emissions in chinchilla ear canals: correlation with histopathology and suppression by external tones. *J Acoust Soc Am* 1984;71:405-9.

22. Schmiedt RA. Acoustic distortion in the ear canal: I. Cubic difference tones: effects of acute noise injury. *J Acoust Soc Am* 1986;79:1481-90.

23. Martin GK, Probst R, Coats AC, Lonsbury-Martin BL. Acoustic distortion products in rabbits. II. Sites of origin revealed by suppression and pure-tone exposures. *Hear Res* 1987;28:191-208.

24. Elberling C, Parbo J, Johnsen NJ, Bagi P. Evoked acoustic emission: clinical application. *Acta Otolaryngol [Suppl]* (Stockh) 1985(suppl 421):77-85.

25. Harris FP, Lonsbury-Martin BL, Stagner BB, Coats AC, Martin GK. Acoustic distortion products in humans: systematic changes in amplitude as a function of f_2/f_1 ratio. *J Acoust Soc Am* 1989;85:220-9.

26. Hallpike CS, Cairns H. Observations on the pathology of Meniere's syndrome. *Proc R Soc Med* 1938;31:1317-36.

27. Nadol JB Jr, Thornton AR. Ultrastructural findings in a case of Meniere's disease. *Ann Otol Rhinol Laryngol* 1987;96:449-54.

28. Bray P, Kemp DT. An advanced cochlear echo technique suitable for infant screening. *Br J Audiol* 1987;21:191-204.

29. Lonsbury-Martin BL, Probst R, Coats AC, Martin GK. Acoustic distortion products in rabbits. I. Basic features and physiological vulnerability. *Hear Res* 1987;28:173-89.

30. Martin GK, Lonsbury-Martin BL, Probst R, Coats AC. Spontaneous otoacoustic emissions in a nonhuman primate. I. Basic features and relations to other emissions. *Hear Res* 1988;33:49-68.

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**SYMPOSIUM ON THE PATHOPHYSIOLOGY OF
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Editor

G. SCOTT GIEBINK, MD

ANNALS
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SYMPOSIUM ON THE PATHOPHYSIOLOGY OF OTITIS MEDIA

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The Symposium on the Pathophysiology of Otitis Media was held December 6, 1988, at the Otitis Media Research Center, University of Minnesota School of Medicine, Minneapolis, Minnesota.

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SYMPOSIUM PARTICIPANTS

Daniel Canafax, PharmD
Associate Professor, Department of Pharmacy
Practice
University of Minnesota College of Pharmacy
Minneapolis, Minnesota

Anna-Mary Carpenter, MD, PhD
Professor Emeritus, Department of Anatomy
University of Minnesota School of Medicine
Minneapolis, Minnesota

G. Scott Giebink, MD
Professor of Pediatrics and Otolaryngology
University of Minnesota School of Medicine
Minneapolis, Minnesota

Marcos Goycoolea, MD, PhD
Research Associate, Department of Otolaryngology
University of Minnesota School of Medicine
Minneapolis, Minnesota

Katsuhisa Ikeda, MD
Visiting Instructor, Department of Otolaryngology
University of Minnesota School of Medicine
Minneapolis, Minnesota

Steven K. Juhn, MD
Professor, Department of Otolaryngology
University of Minnesota School of Medicine
Minneapolis, Minnesota

Timothy T. K. Jung, MD, PhD
Associate Professor, Division of Otolaryngology-
Head and Neck Surgery, Department of Surgery
Loma Linda University
Loma Linda, California

Amy Keller
Medical Research Coordinator
The Upjohn Company
Kalamazoo, Michigan

Chap T. Le, PhD
Associate Professor, Division of Biometry
University of Minnesota School of Public Health
Minneapolis, Minnesota

David J. Lim, MD
Professor, Director of Otological Research
Laboratories
Ohio State University
Columbus, Ohio

Gregory J. Matz, MD
Professor, Department of Otolaryngology
Loyola University Medical Center
Maywood, Illinois

Tetsuo Morizono, MD
Associate Professor, Department of Otolaryngology
University of Minnesota School of Medicine
Minneapolis, Minnesota

Ralph F. Naunton, MD
Director, Division of Communication and
Neurosensory Disorders
National Institutes of Health
Bethesda, Maryland

Michael M. Paparella, MD
Clinical Professor, Department of Otolaryngology
Director, Otopathology Laboratory
University of Minnesota School of Medicine
Minneapolis, Minnesota

Edwin W. Rubel, PhD
Professor of Otolaryngology, Director of Research
University of Washington
Seattle, Washington

Isamu Sando, MD, DMS
Professor of Otolaryngology
Director, Division of Otopathology
University of Pittsburgh
Pittsburgh, Pennsylvania

James Sanford
Medical Sciences Liaison
Infectious Diseases
The Upjohn Company
Minneapolis, Minnesota

Jochen Schacht, PhD
Professor, Department of Otolaryngology
University of Michigan
Ann Arbor, Michigan

Tae H. Yoon, MD
Visiting Instructor, Department of Otolaryngology
University of Minnesota School of Medicine
Minneapolis, Minnesota

INTRODUCTION

This was the second conference on the pathophysiology of otitis media sponsored by the University of Minnesota Otitis Media Research Center, Minneapolis. The first, in December 1986, focused on the biochemical and immunochemical aspects of the disease. This Symposium explored morphologic correlates of the otitis media continuum and inner ear effects of middle ear inflammation and ototoxic drugs.

The past decade has seen an exponential increase in otitis media research, an effort quite consistent with the impact of this disease on child health and adult otic morbidity. Otitis media researchers have taken clinical observations of the disease, as manifested in its many stages, to the laboratory bench for exploration of hypothesized pathophysiologic mechanisms. Animal modeling of otitis media has been a critical element of the laboratory research and has provided the foundation for studying the disease continuum in a controlled fashion, exploring the relative influence of many variables on middle ear morphologic characteristics and function. Collaborative research within and between institutions in the United States and abroad has greatly expanded our understanding of basic disease-producing mechanisms. For example, biochemical studies of middle ear effusion have suggested cellular sources of inflammatory mediators, followed by morphologic confirmation of these sources, leading to physiologic studies of mediator effect on inner ear function. Similarly, the clinical use of antimicrobial drugs both systemically and topically has led to drug efficacy and toxicity concerns that are being addressed in animal studies. This Symposium brought together experts in the fields of otic morphology, biochemistry, physiology, pharmacology, and clinical otology to discuss recent progress in these related disciplines.

The first presentation reviewed otitis media pathophysiology concepts that have guided researchers at the University of Minnesota Research Center since 1974. Morphologic studies of human and animal temporal bones led to the now widely held understanding that otitis media is a disease continuum with many clinical and pathologic stages, to studies of cellular events in middle ear fluid production, to the concept of clinically silent otitis media, and to studies of round window membrane structure and function. Biochemical studies have profiled the myriad inflammatory mediators in effusion and their relationship to mucoperiosteal structure and function. Microbiologic and immunologic research led to the development of acute purulent otitis media animal models, studies of virus infection in otitis media, molecular studies of host-bacteria interaction, and studies with bacterial vaccines to prevent otitis media. Microbial studies led to pharmacology

research in an attempt to understand lack of *in vivo* efficacy of antimicrobial regimens despite apparent *in vitro* bacterial killing, and to develop new treatment approaches. Otophysiologic studies focused on the toxicity of topical antiseptic agents and on the effect of middle ear inflammation on inner ear function. Biometry, in addition to providing core support to the several basic and clinical studies, has successfully developed new analytic methodologies useful to otitis media researchers. Epidemiologic research yielded demographic information on the disease in several population groups and identification of risk factors for disease chronicity. Many investigators, several of whom participated in this Symposium, have contributed to this continuing effort at the University.

In the next paper, Dr Ralph Naunton reviewed National Institutes of Health support of otitis media research, initially via the National Institute of Neurological and Communicative Disorders and Stroke, and now via the new National Institute on Deafness and Other Communication Disorders (NIDCD). Currently, otitis media research receives approximately \$5 million in annual grant support from the NIDCD, and these funds support a broad range of research projects encompassing both clinical and basic science fields.

Dr Anna-Mary Carpenter introduced the discussion of otopathology and noted that any study of tissue morphology begins with a description, proceeds with feasibility studies, and then moves to quantitative studies. Usually the best answer to histologic quantitation comes from a random beginning with systematic sampling thereafter, she noted. With respect to otitis media histology, she emphasized the importance of understanding the types of cells that interact as the concept of time is added to otitis media pathology.

Four papers addressed the otopathology of otitis media through temporal bone studies. Dr Isamu Sando explored the eustachian tubes of children with various congenital craniofacial anomalies, each of whom had evidence of otitis media. A deformity of tubal cartilage was present in nearly half of the cases and tended to be associated with more severe middle ear inflammation. While a causal relationship could not be determined from the study, the data revealed a new aspect of otitis media pathogenesis in children with congenital anomalies.

Drs Michael Paparella, Tae Yoon, Marcos Goycoolea, and colleagues presented three papers on the otitis media continuum as evidenced in temporal bone pathology. In the first, Dr Paparella illustrated changes along the otitis media continuum resulting from longitudinal studies after tubal obstruction in cats, evidence of altered round window

membrane morphologic characteristics during otitis media in cats quite similar to that seen in humans, and changes in the tensor tympani in otitis media. Dr Yoon, using new quantitative and semiquantitative techniques to study temporal bones, found overlapping histopathologic characteristics in middle ear mucosal epithelium and subepithelium in children with various stages of otitis media; these results further strengthened the otitis media continuum hypothesis. Dr Goycoolea discussed round window membrane morphology and permeability from his recently published studies (*Laryngoscope* 1988;98[suppl 44]). He observed that round window membrane morphologic changes in otitis media paralleled middle ear changes, and that the membrane has selectivity barriers that might facilitate the passage of certain molecules into the inner ear. While the morphologic observations do not confirm a functional effect, the findings are consistent with changes in inner ear function in animals and humans with otitis media.

The next presentation, by Dr Timothy Jung, explored the causal effects of arachidonic acid metabolic products on middle ear histopathologic characteristics in an animal model. Prostaglandin and leukotriene metabolites, as well as arachidonic acid derived from phospholipids of cell membranes, inoculated into the ears of chinchillas without obstructed eustachian tubes caused inflammation and effusion; and certain middle ear mucosa histopathologic changes were characteristic of specific metabolites. While relative concentrations of the metabolites after arachidonic acid inoculation might have reflected the relative stability of the end products, this study emphasized the close association between arachidonic acid metabolites in the middle ear and the histopathologic changes of otitis media.

Papers by Drs David Lim and Jochen Schacht discussed the effects of middle ear inflammatory mediators on the inner ear. Endotoxin derived from *Salmonella typhimurium* instilled into the tympanic cavities of chinchillas by Dr Lim and his colleagues was detected in perilymph 12 hours after inoculation, persisted for up to 3 weeks, and caused profound histopathologic changes in perilymphatic spaces, especially in the basal turn. Using an in vitro isolated outer hair cell preparation from guinea pig cochlea, Dr Schacht and coworkers observed an increased rate of hair cell death after incubation with endotoxin and with free radicals — an effect that was delayed by addition of free radical scavengers.

The final five papers explored the pharmacology and toxicity of systemic and ototopical drugs. Dr Gregory Matz reviewed clinical perspectives on ototoxic drugs, noting that salicylates, aminoglycoside antibiotics, loop diuretics, cisplatin, erythromycin, and vancomycin are the most commonly used systemic drugs with ototoxicity. He also reviewed the possible role of topical ear drops as a cause of ototoxicity. Dr Daniel Canafax described the variable middle ear penetration of amoxicillin, trimethoprim, and sulfamethoxazole in the purulent and serous otitis media animal models — evidence that may explain the variable response of children with acute otitis media to antimicrobial therapy.

Advances in ototopical drug toxicity were reviewed next. Dr Tetsuo Morizono studied the effect of several ear drop solutions placed in the middle ear on inner ear function in chinchillas. He found that the short-term toxicity of Coly-Mycin S Otic was twice that of Cortisporin Otic Suspension, and the toxicity of VoSoL Otic Solution was four times that of Cortisporin. Dr Katsuhisa Ikeda extended these studies to include the purulent otitis media animal model. He observed that animals with healed pneumococcal otitis media exhibited less susceptibility to Cortisporin ototoxicity and reduced round window membrane permeability to a medium-sized tracer molecule. This type of modeling separates the conductive from the sensorineural components of hearing loss, since animals are studied after middle ear fluid has resolved. He discussed the currently known factors that affect permeability of the round window membrane. Dr Edwin Rubel closed the discussion by reviewing his experiments in chickens, which have shown that prenatally induced sensorineural hearing loss has a profound effect on cell size in the auditory pathway, whereas conductive loss induced at the same time does not affect cell size.

This 1-day conference contained far more information than one could digest at the time. Most of the participants who made presentations at the meeting were able to submit papers for inclusion in this publication. These can serve present and future researchers and clinicians as they plan laboratory studies, clinical investigations, and patient care.

We are grateful to The Upjohn Company and Glaxo Incorporated for educational grants to publish the proceedings.

G. Scott Giebink, MD
Editor

HISTORICAL PERSPECTIVES AND CONCEPTS IN OTITIS MEDIA RESEARCH AT THE UNIVERSITY OF MINNESOTA

MICHAEL M. PAPARELLA, MD

G. SCOTT GIEBINK, MD

MINNEAPOLIS, MINNESOTA

The University of Minnesota Otitis Media Research Center, formed in 1978, comprises a multidisciplinary research team in the clinical fields of otolaryngology, pediatrics, audiology, and infectious disease as well as the basic science fields of histopathology, epidemiology, microbiology, immunology, biostatistics, pharmacology, physiology, and biochemistry. The team has focused on studies designed to elucidate the pathophysiology of the otitis media continuum, and considerable progress has been made in describing this continuum by using the basic science approaches available in the Center. The collaboration of basic and clinical scientists has created a synergy of goals, ideas, and methods leading to new hypotheses and progress, ultimately resulting in improved patient care methods.

KEY WORDS — multidisciplinary research, otitis media research, pathophysiology.

Studies repeatedly document that otitis media is among the most common childhood diseases in the United States and elsewhere in the world, and that otitis media sequelae are frequent in adults. Until the pioneering work of Dr Ben Senturia, very little serious research was directed toward this common disease. During the past two decades, especially the last decade, basic and applied multidisciplinary otitis media research has blossomed and grown in many centers and universities in the United States and throughout the world under the sponsorship of the National Institutes of Health (NIH). New basic science technologies have been applied to the etiology and pathophysiology of otitis media and to understanding its clinical manifestations. Several international symposia and a plethora of publications document the growth of otitis media research.

The history of otitis media research at the University of Minnesota parallels the history of otitis media research in general during the past two decades; its team of investigators studying the pathogenesis of otitis media is multidisciplinary, including basic and clinical scientists (see Figure). The University of Minnesota Otitis Media Research Center was formed in 1978 on the precept that collaborative efforts from individuals with diverse expertise lead to new insights into pathophysiologic mechanisms and enhance the clinician's ability to diagnose, treat, and prevent otitis media and related conditions. Many investigators have contributed to this research. Those who have moved to other universities continue to provide important insights into this disorder. This historical perspective will consider the present team of investigators at the Center, focusing on their contributions to the development of otitis media research.

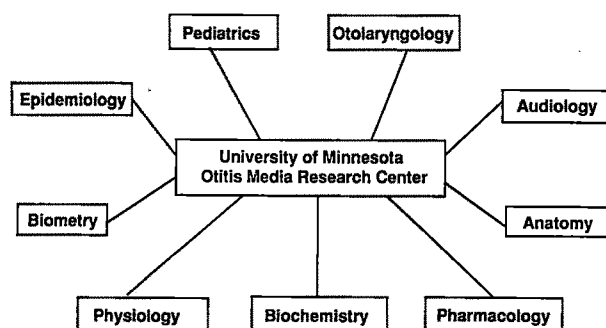
In 1974, collaborative otitis media research was

initiated between Michael Paparella and Steven Juhn in the Otolaryngology Department, and Scott Giebink and Paul Quie in the Pediatrics Department. Subsequently, James Boen (Biometry Division of the School of Public Health), Bill Meyerhoff (Otolaryngology), David Nelson (Otolaryngology), Earl Harford (Audiology), Tetsuo Morizono (Otolaryngology), and Marcos Goycoolea (Otolaryngology) joined the multidisciplinary effort leading to the first NIH/National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)-sponsored Otitis Media Research Center. Administrative leadership of the Center changed from Paparella to Giebink in 1986.

The Center was formed, by a multidisciplinary effort, to investigate the following hypotheses: 1) that the various clinical forms of otitis media represent a continuum of middle ear disease and have common pathophysiologic denominators, 2) that the type and severity of middle ear mucoperiosteal inflammation are reflected in the biochemical composition of middle ear effusion (MEE), 3) that the microbiologic, immunologic, and biochemical profile of effusion at one point in time predicts future middle ear cleft sequelae, 4) that altered round window membrane morphologic characteristics and permeability in otitis media contribute to an accompanying sensorineural hearing loss, 5) that commonly used ototopical antimicrobial agents can cause cochlear injury, 6) that envelope components of pneumococci contribute to chronic otitis media pathogenesis, and 7) that active immunoprophylaxis against the viral and bacterial pathogens causing acute otitis media will prevent the acute disease, thereby blocking the cascade of events leading to chronic otitis media with effusion and intractable pathologic changes.

From the University of Minnesota Otitis Media Research Center (both authors) and the Departments of Otolaryngology (both authors) and Pediatrics (Giebink), University of Minnesota School of Medicine; the Minnesota Ear, Head and Neck Clinic (Paparella); and the International Hearing Foundation (Paparella); Minneapolis, Minnesota. Supported in part by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant 8P50-DC-00133.

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Multidisciplinary team contributing to University of Minnesota Otitis Media Research Center.

OTOLOGY AND OTOPATHOLOGY

Michael Paparella's interest in otitis media pathophysiology was formed from 1961 to 1963, while he was studying the activity of acid and alkaline phosphatases, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase in MEEs from human subjects in Nuremburg, Federal Republic of Germany.¹ Histochemistry was used to localize alkaline phosphatase in middle ear mucoperiosteum biopsy specimens to ascertain the source of the enzyme found in serous fluid. In 1965, while he was at Ohio State University, an NINCDS grant, "Pathogenesis of Serous Otitis Media," supported his research when otitis media was not an NIH priority. Otitis media was modeled in the cat and monkey by use of sterile silicone sponge to obstruct the eustachian tube. Other animal models, including those subjected to barotrauma, were also developed. In these models, a continuum of otitis media was demonstrated in which serous effusion was followed by mucoid effusion, and then by chronic otitis media with cholesterol granulation tissue months later. About that time a visiting otology student, David Lim, understood the importance of otitis media research, and arrangements were made for him to work at Harvard with Bob Kimura. As a result, Lim et al published the first ultrastructural study of the eustachian tube and middle ear mucosa of the guinea pig.²

Paparella's interest in otitis media research persisted with his move, in 1967, to the University of Minnesota. Over the past two decades, he has associated with residents, postdoctoral students, visiting scientists, and clinicians in a number of studies relating to basic and applied otitis media research. His team has observed that sensorineural hearing loss is a complication of chronic otitis media,³ and these observations led to basic research on the ultrastructure of the round window membrane.⁴ Other studies led to reporting cellular events involved in the production of middle ear fluids.⁵ By use of the carbon-labeling technique, clear-cut evidence of plasma transudation from subepithelial vessels was reported in 1972.⁶

The existence of "silent otitis media" was docu-

mented in many animal and human temporal bones among the approximately 500 with otitis media in the Center's otopathology laboratory.⁷ This meant that undetected pathologic changes in the middle ear, particularly chronic changes, could exist behind an intact tympanic membrane. The concept of an otitis media continuum, which had clinical relevance in diagnosing and managing otitis media in patients, was developed. Descriptive histopathologic studies were followed by quantitative and semi-quantitative studies emphasizing the subepithelial space in otitis media.⁸

Clinical studies paralleled the otopathology laboratory research efforts, especially those involving the continuum of otitis media. These included the first published evidence that tympanostomy tubes can prevent recurrent acute otitis media in infants, that insidious inner ear sequelae can result from otitis media, that chronic pathologic conditions can exist behind an intact tympanic membrane and can be treated, that middle ear granulation tissue is important in the otitis media continuum, and that flexible, more conservative methods can be used to treat chronic otitis media, especially in infants.

BIOCHEMISTRY

Steven Juhn joined the University of Minnesota faculty in 1968, after completing his studies with the pioneer of ear biochemistry, Dr Sigurd Rauch, in the Federal Republic of Germany. Juhn helped develop new concepts relating to the biochemistry of middle ear inflammation. Experimental evidence has mounted over the past 20 years under his direction to support the existence of two concepts of otitis media pathogenesis.

The first hypothesis states that the biochemical composition of MEE in otitis media reflects inflammatory changes of the middle ear mucoperiosteum.⁹ Numerous biochemical parameters have been analyzed, and several biochemical characteristics of different types of effusion have been established.¹⁰ In general, enzymatic activity (lactate dehydrogenase, lysozyme, hexosamine) is higher in mucoid than in serous effusion. In experimental purulent otitis media (POM), enzyme levels are higher than in serous effusion induced by obstruction of the eustachian tube. When the two conditions (middle ear inoculation of pathogenic bacteria and obstruction of the eustachian tube) were combined, higher levels of effusion lysozyme were observed than in purulent effusion alone.¹¹

Alpha 2-macroglobulin and leukotriene B₄ were identified as indices of vascular permeability, and levels were higher in effusion from POM than serous otitis media (SOM).¹² A morphologic study using horseradish peroxidase supported this biochemical finding by showing a greater leakage of horseradish peroxidase in POM than in SOM.¹³ The biochemical

composition of effusion in POM also served to evaluate the efficacy of the treatment of otitis media.¹⁴ These biochemical data have supported the hypothesis that mucoperiosteal pathologic processes are reflected in the biochemical composition of MEE. The biochemistry team has not determined, however, the sensitivity of these parameters to the type and severity of mucoperiosteal inflammation, and which specific parameters reflect the chronicity of otitis media.

The second hypothesis states that levels of biochemical components in MEE control the levels of these substances in perilymph. A study of human serum albumin in MEE and perilymph suggested the existence of minimum threshold concentrations for potentially toxic substances in MEE and perilymph.¹⁵ This may explain the variable incidence of sensorineural hearing loss as a complication of otitis media.¹⁶

PEDIATRICS, MICROBIOLOGY, AND IMMUNOLOGY

Scott Giebink and Paul Quie brought expertise in microbiology, immunology, infectious diseases, and clinical pediatrics to the collaborative research effort in 1974. Giebink and his associates developed an animal model for acute POM due to *Streptococcus pneumoniae*, the most common human middle ear pathogen.¹⁷ Since its description in 1976, this model has been used extensively by most otitis media research laboratories in this and other countries.

With the discovery by others that acute otitis media is often caused by respiratory tract viruses, the microbiology group was the first to model this condition in animals. They reported in 1980 a synergy between influenza virus infection of the upper respiratory tract and *S pneumoniae* colonizing the nasopharynx in the development of POM.¹⁸ Subsequently, they reported that not all influenza virus strains have this effect; however, strains that predisposed to POM in the animal model were the same as those that were associated with acute otitis media in humans — an important bridge between the human condition and the animal model.

Jon Abramson, working with the microbiology group and subsequently in Winston-Salem, NC, reported the mechanism by which influenza A viruses impair function of polymorphonuclear leukocytes; these observations have added knowledge to the host defense mechanisms in otitis media and respiratory tract virus infections in general. The studies with influenza virus were carried to the morphologic level with examination of histopathologic changes caused by the virus in the eustachian tube and middle ear. This research suggests that upper respiratory tract viral infection is the principal cause of eustachian tube dysfunction, which precedes POM in humans. Concern with silent otitis media in human studies by the otopathology team led to demonstra-

tion in the chinchilla model that combined infection of the upper respiratory tract with influenza virus and *S pneumoniae* leads, in some cases, to middle ear histopathologic changes characteristic of otitis media without otoscopic or tympanometric signs of the disease.¹⁹

Studies by Giebink and his associates of host response in otitis media have focused on cellular and humoral defenses.²⁰ The research suggested that lysozyme in chronic middle ear fluid is derived more from epithelial cells of the middle ear than from phagocytic cells, and that complement products are not important bacterial chemotaxins for polymorphonuclear leukocytes in the middle ear in this condition.

Early in the collaborative research at Minnesota, the team studied the microbiology and cytology of chronic MEE in children.²¹ Although such a study had been reported previously, this was the first large study (729 children and 1,411 operated ears) and the first to correlate variables such as patient age, treatment, and type of effusion with the bacteriologic and cellular profiles of the effusion. This study led to collaborative research with epidemiologists that resulted in the first report of the epidemiology of chronic otitis media with effusion in children.²² Kathy Daly, an epidemiologist who joined the Center in 1986, studied risk factors for chronic otitis media with effusion and reported that disease laterality, day-care attendance, and effusion duration were the principal factors.²³ This knowledge will permit primary-care clinicians to target certain patients for more aggressive treatment.

In studying the pathogenesis of otitis media, the microbiology team began exploring the role of bacterial subcellular components in causing middle ear inflammation, since the antimicrobial drugs used to treat the purulent phase of the disease may release components of the bacterial cell into the middle ear environment. The team showed in the chinchilla model that *S pneumoniae* cell wall caused both acute and chronic middle ear inflammation, and a similar mechanism may be at the root of chronic otitis media with effusion in humans.²⁴ These results imply that alternate forms of antimicrobial treatment might change the course of otitis media.

Giebink's laboratory pioneered studies on the prevention of otitis media through immunization. In fact, the POM chinchilla animal model was developed with this goal in mind. Early research led to a systematic study of the humoral immune response of chinchillas to *S pneumoniae* capsular polysaccharides.²⁵ This laboratory was the first to demonstrate in an animal model that pneumococcal capsular polysaccharide vaccination prevented type-specific pneumococcal otitis media,²⁶ and this observation led to clinical vaccine trials. Most recently, the laboratory reported that POM can be

prevented by passive immunization with systemically administered immune globulin.²⁷ This is the first clear demonstration that specific immunoglobulin G antibody provides an important antibacterial defense of mucosal surfaces of the respiratory tract — an observation of great importance to the future development of vaccines designed to prevent otitis media.

OTOPHYSIOLOGY

Tetsuo Morizono, an otolaryngologist trained in Japan, joined the University of Minnesota faculty in 1977. Having studied with Brian Johnstone for 10 years in Perth, Australia, Morizono had expertise in basic electrophysiologic techniques that led to his pioneering research on the effects of middle ear ototoxic antiseptics on the inner ear.²⁸ He was the first to describe the effects of solvents and amers of chloramphenicol ear drops with propylene glycol on inner ear function.²⁹ Combined histologic and physiologic studies became possible once he joined the research team.³⁰

Further ototoxicity studies of topical ethanol in animals assessed not only the cochlear microphonic, which is not frequency-specific, but also action potentials, which led to the construction of audiograms and the endocochlear DC potential, which is a descriptor of the function of the stria vascularis.³¹ Many of the studies, such as the investigation of two Betadine preparations, were clinically relevant.³² A study of otic drops with tympanostomy tubes established the existence of sensorineural hearing loss in an animal model of POM,³³ with electrophysiologic documentation³⁴; this study used physiologic methods to study the permeability of the round window membrane.³⁵

ROUND WINDOW MEMBRANE MORPHOLOGY AND FUNCTION

Marcos Goycoolea began studying otitis media in 1975, concomitant with and as an extension of his graduate otolaryngology and doctoral training in anatomy. His subsequent research focused on studying histopathologic changes in middle ear mucosa after inducing otitis media in cats by obstruction of the eustachian tube, and studying the structure, function, and permeability of the round window membrane in animal models and humans. Goycoolea returned to Chile, where he performed epidemiologic research on hearing loss among Easter Island residents. He rejoined the Center in 1985.

Goycoolea et al³⁶ have contributed to otitis media research by describing oval and round window morphologic characteristics in otitis media in the cat. Their longitudinal studies of cellular changes in experimental otitis media³⁷⁻³⁹ included pioneering work on the tensor tympani and stapedius muscle in otitis media.⁴⁰ They were some of the first to study the effect of staphylococcal exotoxin on round win-

dow membrane permeability.⁴¹ He and colleagues identified ganglia and ganglion cells in the cat middle ear and round window membrane.⁴² He and colleagues studied potential pathways between the middle and inner ear⁴³ and demonstrated in chin-chillas that albumin passed from the middle to the inner ear in otitis media through the round window membrane.⁴⁴ He and colleagues⁴⁵ have continued to contribute to our knowledge of middle ear-inner ear relationships with experimental studies of round window membrane structure, function, and permeability.

BIOMETRY

James Boen was the biometrician with the project in 1978, and Chap Le joined the Center as chief biometrician in 1981. In addition to the usual tasks of collaborating with and assisting project investigators in designing studies, setting up and maintaining data bases, and performing statistical analyses, the biometry group has pioneered research in biostatistical methodologies important to future otitis media research.

The fundamental unit for observation as well as for statistical analysis in studies of otitis media is often the ear rather than the person. Frequently, descriptive statistics are computed over distributions of ears, and tests of hypotheses are constructed to compare such distributions. This practice is appropriate when only one ear is used for a given person in any distribution, and standard methods for estimation of parameters and testing of the hypothesis are valid. If the purpose, however, is to compare two different treatments based on findings from ear examinations, then an individual contributes two ears to such an analysis, their values being highly correlated. This intraclass correlation affects statistical analyses and has important implications for the design of research and estimation of sample size. This research had led to reports on the symmetric bivariate binomial distribution and its application to the analysis of clustered samples in medical research,⁴⁶ analysis of nested designs with binomially distributed outcome variables,⁴⁷ testing for linear trends using correlated otolaryngology or ophthalmology data,⁴⁸ and logistic regression analysis for paired Bernoulli outcomes with applications to the risk determination for chronic otitis media (C. T. Le, B. R. Lindgren; unpublished observations, 1988).

PHARMACOLOGY

As basic research led to clinical applications, it became increasingly important to include the discipline of basic and applied pharmacology in the Research Center program, and Daniel Canafax from the College of Pharmacy joined the research group in 1986. The goal of this laboratory is to improve the antibiotic treatment of POM through a better understanding of middle ear drug distribution.

Canafax and his group have completed studies of trimethoprim, sulfamethoxazole, and amoxicillin in microliter volumes of chinchilla MEE and plasma using high-performance liquid chromatography analysis⁴⁹⁻⁵² (also G. R. Erdmann, C. Walker, G. S. Giebink, D. M. Canafax, S. K. Juhn; unpublished observations, 1988). The pharmacology group has focused on studying the penetration of antibiotics into the middle ear and on bacterial killing in the middle ear. Their hypothesis is that response to treatment depends on achieving effective antimicrobial concentrations in MEE, that is, treatment failure is the result of inadequate MEE concentrations over sufficient time. Current studies include dose-ranging experiments, protein binding in plasma and effusion, bacterial killing in effusion after single and multiple antimicrobial drug doses, and correlative studies in the human condition. The collaborative efforts of the pharmacology and microbiology teams suggest that the penetration of antibiotics into the middle ear is variable, and that current dose regimens may be inadequate for bacterial killing in some patients.

CONCLUSION

In summary, research by individual investigators working as a team in the University of Minnesota Otitis Media Research Center has resulted in pioneering discoveries. As always, research ideas have come from many hardworking individuals, too many to mention here; and several have moved to continue their otitis media research at other institutions. Examples of such individuals include Dr Timothy Jung at Loma Linda University, Dr William Meyerhoff at the University of Texas in Dallas, Dr Richard Chole at the University of California-Sacramento, Dr Yasuya Nomura at the University of Tokyo in Japan, and Dr Leonard Rybak at Southern Illinois University. The collaboration of basic and clinical scientists working together creates a synergy of goals, ideas, and methods. Moreover, the team efforts excite and attract new individuals and scientific disciplines, which lead to new hypotheses and progress, ultimately benefiting humankind through improved patient care methods.

REFERENCES

1. Paparella MM, Dito WR. Enzyme studies in serous otitis media. *Arch Otolaryngol* 1964;79:393-8.
2. Lim DJ, Paparella MM, Kimura RS. Ultrastructure of the eustachian tube and middle ear mucosa in the guinea pig. *Acta Otolaryngol (Stockh)* 1967;63:425-44.
3. Paparella MM, Brady DR, Hoel R. Sensorineural hearing loss in chronic otitis media and mastoiditis. *Trans Am Acad Ophthalmol Otolaryngol* 1970;74:108-15.
4. Kawabata I, Paparella MM. Fine structure of the round window membrane. *Ann Otol Rhinol Laryngol* 1971;80:13-26.
5. Paparella MM, Hiraide F, Juhn SK, Kaneko Y. Cellular events involved in middle ear fluid production. *Ann Otol Rhinol Laryngol* 1970;79:766-79.
6. Hiraide F, Paparella MM. Vascular changes in middle ear effusions. *Arch Otolaryngol* 1972;96:45-51.
7. Paparella MM, Shea D, Meyerhoff WL, Goycoolea MV. Silent otitis media. *Laryngoscope* 1980;90:1089-98.
8. Paparella MM, Sipilä P, Juhn SK, Jung TTK. Subepithelial space in otitis media. *Laryngoscope* 1985;95:414-20.
9. Juhn SK, Jung TTK. Inflammatory changes reflected in middle ear effusions. *Auris Nasus Larynx* 1985;12(suppl 1):S63-S66.
10. Juhn SK, Hamaguchi Y, Jung TTK. Biochemistry of middle ear effusion. In: Bernstein J, Ogra P, eds. *Immunology of the ear*. New York, NY: Raven Press, 1987:319-29.
11. Juhn SK, Jung TTK, Giebink GS, Edlin J. Factors involved in the alteration of middle ear effusion composition. In: Lim DJ, ed. *Recent advances in otitis media with effusion*. Philadelphia, Pa: BC Decker, 1984:192-5.
12. Harada T, Juhn SK, Giebink GS. Biochemical parameters reflecting the vascular permeability and inflammatory stage in otitis media. *Otolaryngol Head Neck Surg* 1988;99:160.
13. Sakagami M, Harada T, Juhn SK, Duvall AJ III. Morphologic and biochemical study of vascular permeability of the middle ear mucosa in experimental otitis media. *Ann Otol Rhinol Laryngol* 1990 (in press).
14. Agarwal SP, Edlin J, Juhn SK, Giebink GS. Effects of ampicillin treatment on the biochemical and cytological profiles of experimental purulent otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. *Recent advances in otitis media*. Toronto, Canada: BC Decker, 1988:228-31.
15. Juhn SK, Hamaguchi Y, Morizono T. Relationship between middle ear inflammation and round window membrane permeability in antigen-induced otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. *Recent advances in otitis media*. Toronto, Canada: BC Decker, 1988:425-8.
16. Juhn SK. Barrier systems in the inner ear. *Acta Otolaryngol [Suppl] (Stockh)* 1988(suppl 458):79-83.
17. Giebink GS, Payne EE, Mills EL, Juhn SK, Quie PG. Experimental otitis media due to *Streptococcus pneumoniae*: immunopathogenic response in the chinchilla. *J Infect Dis* 1976;134:595-604.
18. Giebink GS, Berzins IK, Marker SC, Schiffman G. Experimental otitis media after nasal inoculation of *Streptococcus pneumoniae* and influenza A virus in chinchillas. *Infect Immun* 1980;30:445-50.
19. Giebink GS, Ripley ML, Shea DA, Wright PF, Paparella MM. Clinical-histopathological correlations in experimental otitis media: implications for silent otitis media in humans. *Pediatr Res* 1985;19:389-97.
20. Giebink GS, Carlson BA, Hetherington SV, Hostetter MK, Le CT, Juhn SK. Bacterial and polymorphonuclear leukocyte contribution to middle ear inflammation in chronic otitis media with effusion. *Ann Otol Rhinol Laryngol* 1985;94:398-402.
21. Giebink GS, Juhn SK, Weber ML, Le CT. The bacteriology and cytology of chronic otitis media with effusion. *Pediatr Infect Dis* 1982;1:98-103.
22. Giebink GS, Le CT, Paparella MM. Epidemiology of otitis media with effusion in children. *Arch Otolaryngol* 1982;108:563-6.
23. Daly K, Giebink GS, Le CT, et al. Risk determination for chronic otitis media with effusion. *Pediatr Infect Dis* 1988;7:471-5.
24. Ripley-Petzoldt ML, Giebink GS, Juhn SK, Aeppli D, Tomasz A, Tuomanen E. The contribution of pneumococcal cell wall to the pathogenesis of experimental otitis media. *J Infect Dis* 1988;157:245-55.

25. Giebink GS, Schiffman G. Humoral immune response in chinchillas to the capsular polysaccharides of *Streptococcus pneumoniae*. *Infect Immun* 1983;39:638-44.
26. Giebink GS, Berzins IK, Schiffman G, Quie PG. Experimental otitis media following nasal colonization with type 7F *Streptococcus pneumoniae*: prevention after vaccination with pneumococcal capsular polysaccharide. *J Infect Dis* 1979;140:716-23.
27. Shurin PA, Giebink GS, Wegman DL, et al. Prevention of pneumococcal otitis media in chinchillas with human bacterial polysaccharide immune globulin. *J Clin Microbiol* 1988;26:755-9.
28. Morizono T, Johnstone BM, Entjep H. The ototoxicity of antiseptics (preliminary report). *J Otolaryngol Soc Aust* 1973;3:550-3.
29. Morizono T, Johnstone BM. Ototoxicity of chloramphenicol eardrops with propylene glycol as solvent. *Med J Aust* 1975;2:634-8.
30. Morizono T, Paparella MM, Juhn SK. Ototoxicity of propylene glycol in experimental animals. *Am J Otol* 1980;1:393-9.
31. Morizono T, Sikora M. Ototoxicity of ethanol in the tympanic cleft in animals. *Acta Otolaryngol (Stockh)* 1981;92:33-40.
32. Morizono T, Sikora J. Ototoxicity of povidone-iodine (Betadine) applied in the tympanic cleft in chinchillas. *Arch Otolaryngol* 1982;108:210-3.
33. Meyerhoff WL, Morizono T, Wright CG, Shaddock LC, Shea D, Sikora MA. Tympanostomy tubes and otic drops. *Laryngoscope* 1983;93:1022-7.
34. Morizono T, Giebink GS, Sikora MA, Paparella MM. Sensorineural hearing loss in an animal model of purulent otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media. Toronto, Canada: BC Decker, 1988:341-4.
35. Ikeda K, Morizono T. The changes of the round window membrane permeability in otitis media. *Arch Otolaryngol Head Neck Surg* 1988;114:895-7.
36. Goycoolea MV, Paparella MM, Carpenter A-M, Juhn SK. Oval and round window changes in otitis media: an experimental study in the cat. *Surg Forum* 1978;29:578-80.
37. Goycoolea MV, Paparella MM, Carpenter A-M, Juhn SK. A longitudinal study of cellular changes in experimental otitis media. *Otolaryngol Head Neck Surg* 1979;87:685-700.
38. Goycoolea MV, Paparella MM, Goldberg G, Carpenter A-M. Permeability of the round window membrane in otitis media. *Arch Otolaryngol* 1980;106:430-3.
39. Goycoolea MV, Paparella MM, Juhn SK, Carpenter A-M. Cells involved in the middle ear defense system. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):121-8.
40. Goycoolea MV, Paparella MM, Carpenter A-M. Infiltration of the tensor tympani muscle and stapedius muscles in otitis media. An experimental study in the cat. *Int J Pediatr Otorhinolaryngol* 1979;1:231-9.
41. Goycoolea MV, Paparella MM, Goldberg B, Schlievert PM, Carpenter A-M. Permeability of the middle ear to staphylococcal pyrogenic exotoxin in otitis media. *Int J Pediatr Otorhinolaryngol* 1980;1:301-8.
42. Goycoolea MV, Carpenter A-M, Paparella MM, Juhn SK. Ganglia and ganglion cells in the middle ear of the cat: preliminary report. *Arch Otolaryngol* 1980;106:269-71.
43. Goycoolea MV, Paparella MM, Carpenter A-M. Oval and round window changes in otitis media: potential pathways between middle and inner ear. *Laryngoscope* 1980;90:1387-91.
44. Goldberg B, Goycoolea MV, Schlievert PM, et al. Passage of albumin from middle ear to inner ear in otitis media: an experimental study in the chinchilla. *Am J Otol* 1981;2:210-4.
45. Goycoolea MV, Muchow D, Schachern P. Experimental studies on round window membrane structure, function, and permeability. *Laryngoscope* 1988;98(suppl 44).
46. Le CT. A symmetric bivariate binomial distribution and its applications to the analysis of clustered samples in medical research. *Biom J* 1984;26:289-94.
47. Le CT. Analysis of nested designs with binomially-distributed outcome variables. *Biom J* 1987;29:153-61.
48. Le CT. Testing for linear trends using correlated otolaryngology or ophthalmology data. *Biometrics* 1988;44:299-303.
49. Erdmann GR, Canafax DM, Giebink GS. High-performance liquid chromatographic analysis of trimethoprim and sulfamethoxazole in microliter volumes of chinchilla middle ear effusion and serum. *J Chromatogr* 1988;433:187-95.
50. Canafax DM, Giebink GS, Erdmann GR, Cipolle RJ, Juhn SK. Penetration of trimethoprim and sulfamethoxazole into the middle ear in experimental otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media. Toronto, Canada: BC Decker, 1988:219-22.
51. Canafax DM, Nonomura N, Erdmann GR, Le CT, Juhn SK, Giebink GS. Experimental animal models for studying antimicrobial pharmacokinetics in otitis media. *Pharm Res* 1989;6:279-85.
52. Giebink GS, Canafax DM. Controversies in the management of acute otitis media. In: Aronoff SC, Hughes WT, Kohl S, Speck WT, Wald ER, eds. Advances in pediatric infectious diseases. Vol 3. Chicago, Ill: Year Book Medical Publishers, 1988:47-63.

OTITIS MEDIA RESEARCH: THE NIH PERSPECTIVE

RALPH F. NAUNTON, MD

BETHESDA, MARYLAND

The National Institutes of Health have supported research on otitis media for a number of years, primarily via the National Institute of Neurological and Communicative Disorders and Stroke. There is now a separate Institute on Deafness and Other Communication Disorders (NIDCD), which is firmly committed to continue support for studies of otitis media as in the past, perhaps even at an increased level as funds permit.

Currently, otitis media receives approximately \$5 million in grant support for research in various fields of investigation. Pharmacologic studies, such as that of the efficacy of single daily doses of antibiotics in preventing acute otitis media and the long-term prevention of otitis media with effusion, and that of the relative value of 10 as opposed to 20 days of antibiotic treatment for acute suppurative otitis media, are presently supported. Studies related to clinical practice, such as a comparison of adenoidectomy alone and adenoidectomy with tonsillectomy in the treatment of recurrent otitis media, are funded. In the field of epidemiology, the National Institutes of Health/NIDCD support studies of otitis media with particular attention to passive smoking, attendance in day-care programs, feeding practices, and effects on language development and learning. A number of histopathologic studies are funded, including the following: morphometric and immunohistochemical studies of temporal bones from subjects with a history of otitis media or anomalies likely to affect middle ear structure, anatomic studies of structures associated with the eustachian tube (cartilage, lumen, tensor and levator veli palatini muscles), studies of eustachian

tube changes with advancing age, studies of artificially induced cholesteatoma, and in vitro studies of keratinocyte proliferation and differentiation. Ototoxicity studies of the adverse inner ear effects of topical medications commonly used in the treatment of otitis media are supported, as well as development of a model of chronic suppurative otitis media. Numerous microbiologic studies are funded and include investigations into the following: aspects of middle ear immune response, including the production of various types of immunoglobulin; the potential existence of specific lymphocyte homing to the middle ear mucosa, and the role of the eustachian tube in antigen clearance; the role of complement in otitis media with effusion; the immunocytochemistry of pneumococcal antigens; factors determining the physical characteristics of middle ear effusions; the activity of hydrolase in the normal and diseased middle ear; attachment of nontypeable *Hemophilus influenzae* to the mucosa of the middle ear, studied by use of monoclonal antibodies to isolated fimbriae; ciliary activity in in vivo explants of middle ear mucosa maintained in tissue culture; and the role of viral enhancement of bacterial infection in the middle ear.

This impressive but incomplete list of studies under way leaves plenty of room for expansion of this particular area of study — and room for more applications to the NIDCD. I hope that this brief introduction, and the presentations that follow, will provide inspiration toward further research efforts leading to a better understanding of otitis media in all its varieties, and better preventive and therapeutic measures for future patients.

OTITIS MEDIA IN ASSOCIATION WITH VARIOUS CONGENITAL DISEASES PRELIMINARY STUDY

ISAMU SANDO, MD, DMS

HARUO TAKAHASHI, MD

PITTSBURGH, PENNSYLVANIA

We studied temporal bone histopathology to obtain clues as to the role of eustachian tube (ET) disease in the pathogenesis of otitis media (OM) in patients with congenital anomalies. Thirteen temporal bones obtained from 13 individuals with various congenital anomalies were used. We looked in particular at severity of inflammation in the middle ear (ME) and ET, and at deformity of the ET cartilage. Evidence of OM was found in all the temporal bones. The ETs consistently showed a moderate degree of inflammation but without any particular correlation with the severity of ME inflammation. Deformity of the ET cartilage was present in six cases (46.2%), representing three cases of cleft palate and three of other congenital anomalies. Because the deformity of ET cartilage tended to be associated with more severe OM, we consider this cartilage deformity to be an important cause of tubal dysfunction, and thus of the high incidence of OM among individuals with congenital ear anomalies.

KEY WORDS — cartilage, cleft palate, congenital anomaly, eustachian tube, histopathology, otitis media, temporal bone.

INTRODUCTION

Although it is well known that the eustachian tube (ET) plays an important role in the pathogenesis of otitis media (OM),^{1,2} there have been only a few histopathologic studies of the relation of OM to ET disorders in humans.³⁻⁵ On the other hand, it is well known that individuals with congenital anomalies such as cleft palate^{6,7} or Down syndrome^{8,9} more often experience ET dysfunction and OM than do individuals without these anomalies. Deformity of the ET cartilage has been reported as one of the possible causes of OM in the cleft palate cases.^{10,11} However, the cause of OM in these cases is still controversial.

Because an analysis of the disorders of the middle ear (ME) together with that of the ET in cases of OM is essential in understanding the pathogenesis of OM, we undertook this study to investigate possible correlations between OM and ET disorders in individuals with congenital anomalies.

MATERIALS AND METHODS

The materials used were 13 temporal bones with the ETs and their surrounding structures attached, which were obtained from 13 children with various congenital anomalies, 1 month to 6 years of age (mean, 1.30 ± 1.61 years). The anomalies present are shown in the Table. The temporal bones were

EUSTACHIAN TUBE CARTILAGE ANOMALIES AND MIDDLE EAR INFLAMMATION IN TEMPORAL BONES OF INDIVIDUALS WITH CONGENITAL ANOMALIES

Case No.	Age	Sex	Side	Grade of Inflammation			Anomaly of ETC	Underlying Diseases
				ET1	ET2	ME		
1	1 mo	F	L	II	III	III	(+)	Cleft palate
2	1 yr	F	L	III	III	III	(+)	Cleft palate
3	1.5 mo	F	L	III	III	III	(+)	Cleft palate
4	6 mo	F	L	II	II	II	(-)	Down syndrome
5	1 yr	F	L	II	I	I	(+)	Down syndrome
6	1 yr 1 mo	M	L	II	II	II	(+)	Down syndrome
7	1 yr 5 mo	F	L	II	III	III	(-)	MCA
8	4 mo	M	L	I	I	II	(-)	Tetralogy of Fallot
9	6 yr	F	L	II	II	I	(-)	Biliary atresia
10	3 yr 7 mo	M	L	II	II	I	(-)	Alagille's syndrome
11	1 yr	F	L	II	I	I	(-)	Giant facial hemangioma
12	9 mo	M	L	III	II	I	(+)	MCA
13	1 mo	F	L	II	I	I	(-)	MCA

ET1 — midcartilaginous portion of eustachian tube, ET2 — isthmus portion of eustachian tube, ME — middle ear, ETC — eustachian tube cartilage, MCA — multiple congenital anomalies.

From the Department of Otolaryngology, University of Pittsburgh School of Medicine, Eye and Ear Hospital of Pittsburgh, Pittsburgh, Pennsylvania. Supported by grant DC-00158 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

REPRINTS — Isamu Sando, MD, DMS, Eye and Ear Institute, 203 Lothrop St, Room 153, Pittsburgh, PA 15213.



Fig 1. Local and sparse mononuclear cell infiltration (arrows) in submucosal layer in grade I inflammation of A) middle ear and B) eustachian tube.

removed at autopsy, fixed in 10% formaldehyde solution, decalcified in trichloroacetic acid, dehydrated in graded concentrations of ethanol, embedded in celloidin, and sectioned vertically at a thickness of 20 to 30 μm . Every 20th section was stained with hematoxylin and eosin and examined under the light microscope.

The severity of inflammation in the ME and the ET was investigated in all cases. The severity of ME inflammation was examined histologically in a section that included the promontory,^{12,13} and in those that contained a midcartilaginous portion and an isthmus portion. The degree of mononuclear cell in-

filtration in the submucosal layer was graded as follows: grade 0, almost no infiltration; grade I, local, sparse infiltration (Fig 1); grade II, focal, dense infiltration (Fig 2); and grade III, diffuse, dense infiltration (Fig 3).

The incidence and severity of OM was analyzed in relation to the underlying anomalies. An anomaly of the ET cartilage was sought in each case by examination of the angle between the tangential lines of the inner surface (that facing the ET lumen) of the lateral lamina and the superior half of the medial lamina at the midcartilaginous portion (Fig 4). The severity of OM was compared in ears with and

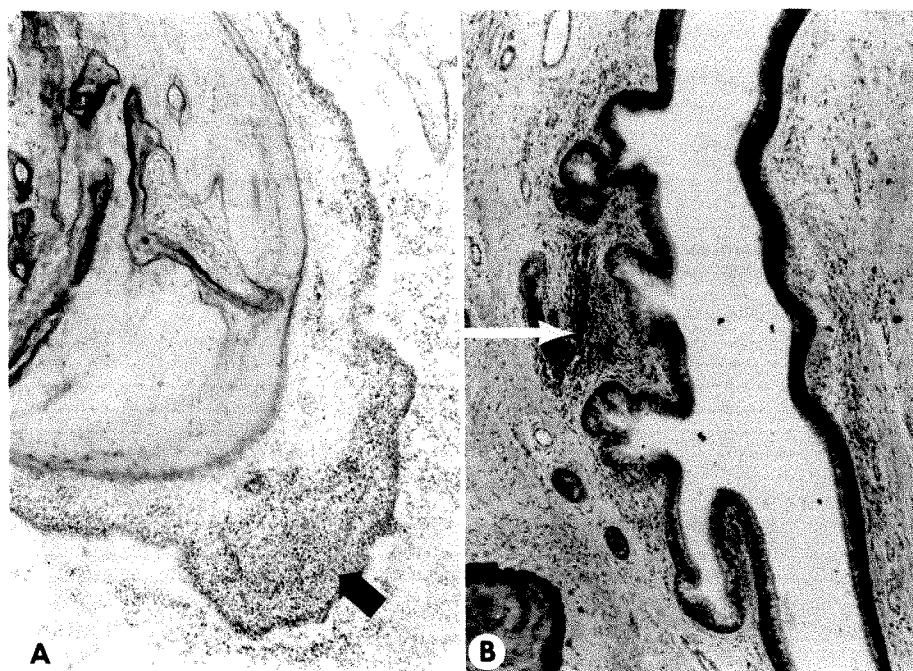


Fig 2. Focal and dense mononuclear cell infiltration (arrows) in submucosal layer in grade II inflammation of A) middle ear and B) eustachian tube.

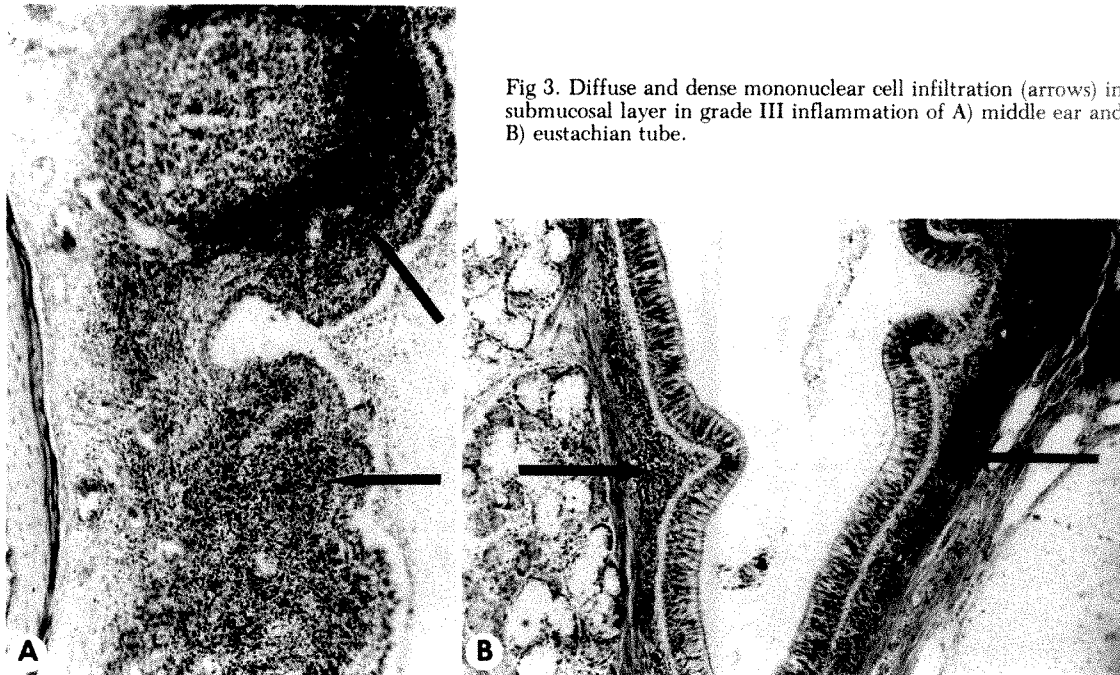


Fig 3. Diffuse and dense mononuclear cell infiltration (arrows) in submucosal layer in grade III inflammation of A) middle ear and B) eustachian tube.

without an anomaly of the ET cartilage.

RESULTS

The severity of inflammation in the ME and ET in the presence or absence of an anomaly of the ET cartilage is shown in the Table. All cases had OM of some degree, and all showed ET inflammation (Fig 5). There was a tendency for the ET (especially the midcartilaginous portion) to be moderately inflamed (grade II), whatever the grade of inflammation present in the ME, although the severity of inflammation of the isthmus portion was somewhat related to the grade of OM.

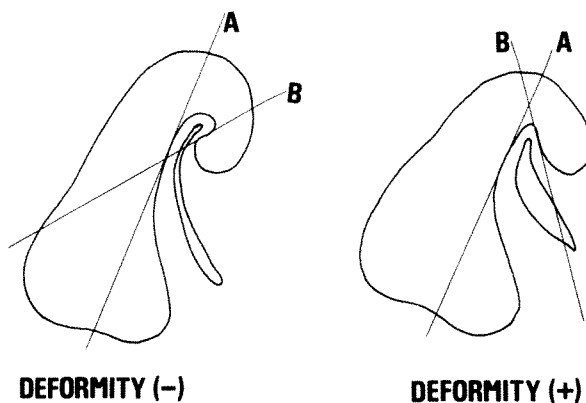
All three specimens from individuals with cleft palate had the highest grade of OM, while in most

other cases (90.0%), low-grade OM was present (Fig 6).

A deformity (anomaly) of the ET cartilage was seen in six cases (46.2%). This anomaly was present in all three cases of cleft palate, in two of the three cases of Down syndrome, and in one of the three multiple congenital anomaly cases. The OM was more severe in cases of deformity of the ET cartilage (Fig 7).

DISCUSSION

The histopathologic features of OM include vascular changes (dilatation and proliferation), cellular infiltrative changes (mononuclear cell infiltration), epithelial changes (thickening and metaplasia), glandular changes (gland formation), and exudative changes (edema and exudation).^{3,4,14,15} Of



DEFORMITY (-)

DEFORMITY (+)

Fig 4. Measurement of eustachian tube cartilage to see if deformity is present. When angle between lines along upper half of luminal side of medial lamina (A) and luminal side of lateral lamina (B) closes inferiorly or two lines are parallel, cartilage is considered normal. When angle between lines A and B opens inferiorly, cartilage is considered deformed.

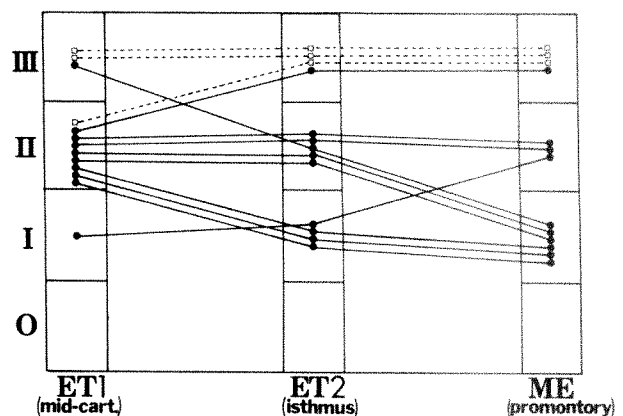


Fig 5. Severity of inflammation in midcartilaginous portion (mid-cart) of eustachian tube (ET), isthmus portion of ET, and middle ear promontory (ME) in 13 cases. White squares and dashed lines — cleft palate cases.

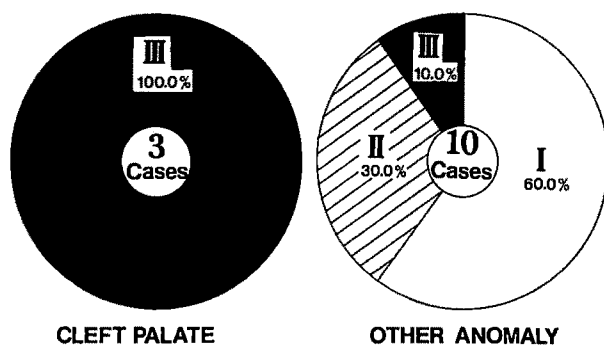


Fig 6. Severity of otitis media in cleft palate cases and other anomaly cases.

these, cellular infiltrative changes are considered the best index for quantitating inflammation, because these changes occur promptly in response to inflammation, and because they occur with both acute and chronic inflammation. In addition, infiltrative changes are not affected by specimen processing, as is an inflammatory exudate, and these changes do not need to be examined by special staining techniques, as secretory gland changes do.

Berger et al⁵ examined the degree of inflammation of the ME and ET in individuals with OM and found that the inflammatory reaction was greater in the ME than in the ET and that the reaction diminished toward the pharyngeal portion. Our results, however, indicate that the midcartilaginous portion of the ET consistently showed moderate in-

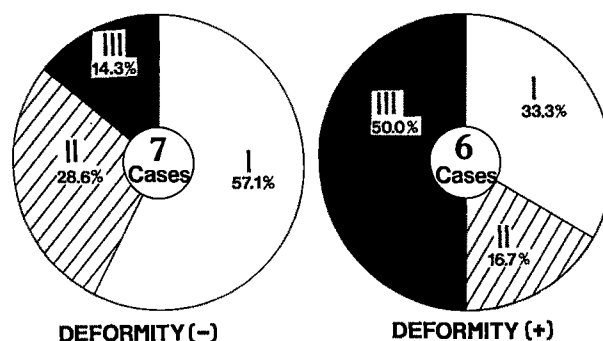


Fig 7. Correlation between severity of otitis media and deformity of tubal cartilage.

flammation that did not correlate with the degree of ME inflammation. This constant degree of cell infiltration in the midcartilaginous portion of the ET may be a defense mechanism against ascending infectious agents; or the inflammatory reaction in the ME may affect the ET as far down as its isthmus portion.

A deformity of the ET cartilage was seen in all three cases of cleft palate and in three cases of other congenital anomalies. Although this deformity has been reported clinically¹¹ and histopathologically,¹⁰ our finding that OM is more severe in such ears seems to make the relationship between the deformity of ET cartilage and OM clearer, and to reveal a new aspect of OM pathogenesis in children with congenital anomalies.

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REFERENCES

1. Bluestone CD, Beery QC, Paradise JL. Symposium on prophylaxis and treatment of middle ear effusions: IV. Physiology of the eustachian tube in the pathogenesis and management of middle ear effusions. *Laryngoscope* 1972;82:1654-70.
2. Silverstein H, Miller GF. Eustachian tube dysfunction as a cause for chronic secretory otitis in children. *Laryngoscope* 1966;76:259-73.
3. Schuknecht HF, Kerr AG. Pathology of the eustachian tube. *Arch Otolaryngol* 1967;86:497-502.
4. Sadé J. Pathology and pathogenesis of serous otitis media. *Arch Otolaryngol* 1966;84:297-305.
5. Berger G, Sadé J, Sachs Z, et al. The involvement of the eustachian tube mucosal lining in acute and secretory otitis media. In: Sadé J, ed. *The eustachian tube*. Amsterdam, the Netherlands: Kugler, 1987:55-61.
6. Kitajiri M, Sando I, Hashida Y, Doyle WJ. Histopathology of otitis media in infants with cleft and high-arched palates. *Ann Otol Rhinol Laryngol* 1985;94:44-50.
7. Bluestone CD. Eustachian tube obstruction in the infant with cleft palate. *Ann Otol Rhinol Laryngol* 1971;80(suppl 2).
8. White BL, Doyle W, Bluestone CD. Eustachian tube function in infants and children with Down syndrome. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. *Recent advances in otitis media*. Philadelphia, Pa: BC Decker, 1984:62-6.
9. Shibahara Y, Sando I. Congenital anomalies of the eustachian tube in Down syndrome. *Histopathologic case report*. *Ann Otol Rhinol Laryngol* 1989;98:543-7.
10. Shibahara Y, Sando I. Histopathologic study of eustachian tube in cleft palate patients. *Ann Otol Rhinol Laryngol* 1988;97:403-8.
11. Naito Y, Tasaka Y, Honjo I, et al. Magnetic resonance imaging of cleft palate. *Pract Otol (Kyoto)* 1987;80:435-40.
12. Sando I, Doyle WJ, Okuno H, Takahara T, Kitajiri M, Coury WJ III. A method for the histopathological analysis of the temporal bone and the eustachian tube and its accessory structures. *Ann Otol Rhinol Laryngol* 1986;95:267-74.
13. Takahara T, Sando I. The common site for otitis media in human temporal bones — a quantitative histopathological study. *Auris Nasus Larynx* 1985;12(suppl 1):173-6.
14. Robbins SL, Kumar V. *Basic pathology*. 4th ed. Philadelphia, Pa: WB Saunders, 1987:28-61.
15. Tos M, Bak-Pedersen K. The outlet of chronic secretory otitis media. *Arch Otolaryngol* 1975;101:123-8.

OTOPATHOLOGIC CORRELATES OF THE CONTINUUM OF OTITIS MEDIA

MICHAEL M. PAPARELLA, MD
MOHAMED M. ABDELHAMMID, MD

PATRICIA A. SCHACHERN
RANA SAHNI, MD
MINNEAPOLIS, MINNESOTA

TAE H. YOON, MD
SADY S. DA COSTA, MD

It has been our hypothesis that different types of middle ear effusions and the clinical manifestations with which they are associated represent the typical inflammatory response. Employing an animal model under controlled conditions, we present statistical evidence that change in the mucosa of the middle ear in otitis media can occur along a continuum, with early forms regressing to more chronic stages of the disease. We also demonstrate an increase in the thickness and a decrease in the permeability of the round window membrane in a longitudinal study of otitis media in the same animal model. Histopathologic changes in human temporal bones with otitis media with effusion or chronic otitis media are similar to the changes in the animal models. These results support a concept that all categories of otitis media (serous, purulent, mucoid, and chronic) represent different stages in a continuum of events.

KEY WORDS — continuum of otitis media, middle ear effusion, morphometry.

INTRODUCTION

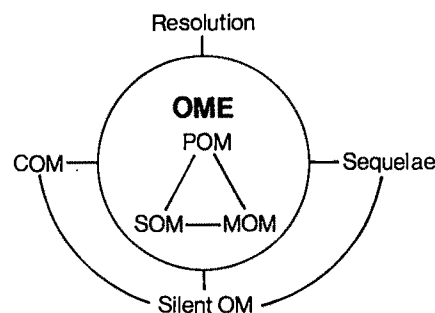
It has been our hypothesis that all categories of otitis media (serous, purulent, mucoid, and chronic) represent different stages in a continuum of events (see Figure). We first described the continuum of mucoperiosteal changes leading to chronic inflammatory disease in 1970 in a study of otitis media induced by obstruction of the eustachian tube in squirrel monkeys.¹ This model of tubal obstruction, with variations in materials and objectives, has been repeated in various species many times.²⁻⁵

Increased permeability of vessels in the middle ears of monkeys began 24 hours after obstruction, peaked at 2 days, and continued with less intensity for 1 month.² In a multidisciplinary study, we compared histologic changes in the middle ear mucosa and biochemical findings of middle ear effusions using chinchillas, cats, and humans with serous, mucoid, and chronic otitis medias.³ Histologic and biochemical similarities within the categories of otitis media among the animal species supported our theory of an otitis media continuum.

To further investigate our hypothesis, we examined the continuum of mucoperiosteal changes in cats studied longitudinally from 1 day to 6 months after eustachian tube obstruction.⁴ Changes were gradual, and the type of otitis media changed from serous to purulent to mucoid and, finally, to chronic. In these animals, we also examined cellular infiltration of the tensor tympani and stapedius muscles. Changes in connective tissue (perimysium and endomysium) in these muscles followed sequential changes in the mucoperiosteum in the middle ear,

although to a lesser degree.⁵

Although these studies, which relied on gross histopathologic descriptions, yielded important information regarding the pathology and pathogenesis of otitis media, quantitative and semiquantitative histology was necessary to make pathologic and morphologic descriptions statistically measurable. Previous morphometric studies of the middle ear have been few and have concentrated principally on components of the epithelial layer, such as the goblet cell and mucous gland, and have described cellular types and distribution.⁶⁻⁸ Only a few investigators have studied morphometric changes in the subepithelial layer.^{9,10} Because histopathologic characterization of the middle ear in otitis media is extremely important and has been only partially explored, we report here results of quantitative and semiquantitative mapping of the middle ear cleft



Continuum of otitis media and interaction of its various forms. OME — otitis media with effusion, POM — purulent otitis media, SOM — serous otitis media, MOM — mucoid otitis media, COM — chronic otitis media, OM — otitis media.

From the University of Minnesota Otitis Media Research Center and the Department of Otolaryngology, University of Minnesota School of Medicine (Paparella, Schachern, Yoon); the Minnesota Ear, Head and Neck Clinic (Paparella, Sahni); and the International Hearing Foundation (Abdelhammid, da Costa); Minneapolis, Minnesota. Supported in part by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant 8P50-DC-00133, the International Hearing Foundation, and the Deafness Research Foundation. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota. REPRINTS — Michael M. Paparella, MD, Minnesota Ear, Head and Neck Clinic, 701 25th Ave S, Minneapolis, MN 55454.

TABLE 1. TYPES OF EFFUSION AND INTRACTABLE CHANGES IN TISSUE IN DIFFERENT STAGES OF OTITIS MEDIA

Stage of Otitis Media	No. of Ears	Type of Effusion					No. of Ears with Intractable Changes in Tissue
		S	SP	P	MP	M	
Acute early (1 to 3 d)	9	4	4	1	0	0	0
Acute late (1 to 3 wk)	9	1	0	8	0	0	2
Subacute (4 to 5 wk)	6	0	0	2	2	2	4
Chronic (3 to 6 mo)	5	1	0	0	1	3	5
Total	29	6	4	11	3	5	11

S — serous, SP — seropurulent, P — purulent, MP — mucopurulent, M — mucoid.

for the various categories of otitis media as seen in temporal bones from humans and animal models.

ANIMAL MORPHOMETRY

Longitudinal Study of Otitis Media in Cats. The eustachian tubes of 29 cats were obstructed unilaterally. Nine animals were killed painlessly at 1 to 3 days after obstruction (acute early stage), nine at 1 to 3 weeks after obstruction (acute late stage), six at 4 to 5 weeks after obstruction (subacute stage), and five at 3 to 6 months after obstruction (chronic stage). The classification of otitis media stages was based on a modification of the classification suggested by the Ad Hoc Committee on Definition and Classification of Otitis Media.¹¹ Temporal bones from five nonobstructed cats (10 ears) were processed as controls. Measurements at the promontory were made of epithelial and subepithelial layers in the middle ear mucosa. Samples were measured at the bony wall extending laterally from the basilar membrane of the basal turn at the level of the hook end of the cochlea as well as at two points adjacent, at a magnification of 1,000x, by use of a calibrated eyepiece micrometer.

Cellular changes in the epithelial layer were measured as percentages of each type of epithelial cell (eg, goblet cells, ciliated cells) among total numbers of epithelial cells within a 100- μ m length of the epithelial layer. Subepithelial measurements included

thickness, vasodilatation, vascularization, fibroblastic reaction, and inflammatory cell infiltration. Mean values for all groups were compared. The mean value of change for each group was calculated by measuring the actual change between the left and right ear of each subject. Analysis of variance was used to compare means from all groups for each location. If a significant F ($p < .05$) was obtained, then the 95% confidence intervals of the true means were compared.

Serous and seropurulent effusion was observed in the acute early stage, purulent effusion in the acute late stage, and mucopurulent or mucoid effusion in the subacute or chronic stage (Table 1).

The majority of promontory epithelial cells were squamous, with some areas of cuboidal and ciliated cells in normal middle ears. Metaplasia of cuboidal cells in the otitis medias began in the acute late stage, continued in the subacute stage, and decreased slightly in the chronic stage (Table 2). The increase in cuboidal cells was statistically significant only in the acute late stage compared with the normal. Goblet cells increased in the acute late stage, increased severely in the subacute stage, and decreased slightly in the chronic stage. Although a significant increase in goblet cells was observed in the acute late and subacute stages compared to the normal, there was no statistical difference between the two stages of otitis media. Increases in columnar and ciliated cells were mild in the acute late stage, moderate in the subacute stage, and severe in the chronic stage, but these increases were not statistically significant.

An increased thickness of the subepithelial space was seen in all stages of otitis media (Table 3). Thickness was mildly increased in the acute early stage, moderately increased in the acute late stage, and severely increased in the subacute stage and chronic stages. Changes in thickness in groups with otitis media were statistically significant compared to those in controls. There was no significant difference among adjacent groups with otitis media.

Changes in density of inflammatory cells were statistically significant when groups in the acute late and subacute stages were compared with con-

TABLE 2. CHANGES IN EPITHELIUM AT PROMONTORY

Stages of Otitis Media	No. of Ears	Cell Type			
		Cuboidal (%)	Columnar (%)	Goblet (%)	Ciliated (%)
Controls	5	0.6 $\pm$ 2.7	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
Acute early	9	0.5 $\pm$ 23.7	0.9 $\pm$ 2.9	0 $\pm$ 0	-2.2 $\pm$ 16.1
Acute late	9	32.9 $\pm$ 19.4*	5.7 $\pm$ 10.2	4.0 $\pm$ 3.9*	16.0 $\pm$ 35.3
Subacute	6	31.8 $\pm$ 36.9	8.0 $\pm$ 9.6	13.7 $\pm$ 13.0	27.0 $\pm$ 30.5
Chronic	5	17.5 $\pm$ 20.5	27.5 $\pm$ 39.2	4.0 $\pm$ 3.2	33.8 $\pm$ 32.1
Significance of differences among otitis media types		<.05	NS	<.01	NS

Values represent mean $\pm$ SD.
 MS — not statistically significant.
 *Statistically different from control group ($p < .05$).

TABLE 3. CHANGES IN SUBEPITHELIAL SPACE AT PROMONTORY

Stages of Otitis Media	No. of Ears	Thickness (μ m)	Categories			
			Inflammatory Cell Density (No./HPF)	Fibroblast Density (No./HPF)	Vascularization (No.)	Vasodilatation (%)
Controls	5	0.2 $\pm$ 4.2	-8.7 $\pm$ 21.6	-7.8 $\pm$ 39.0	0.2 $\pm$ 0.6	0 $\pm$ 0
Acute early	9	19.6 $\pm$ 13.9*	30.0 $\pm$ 33.3	-8.1 $\pm$ 8.4	0.9 $\pm$ 0.8	4.6 $\pm$ 7.1
Acute late	9	135.8 $\pm$ 149.1*	261.9 $\pm$ 129.9*	34.2 $\pm$ 57.0	3.5 $\pm$ 3.2*	28.2 $\pm$ 19.2*
Subacute	6	378.9 $\pm$ 286.5*	146.1 $\pm$ 47.7*	43.5 $\pm$ 40.8	8.7 $\pm$ 4.1*	19.7 $\pm$ 12.7*
Chronic	5	233.4 $\pm$ 118.3*	120.0 $\pm$ 84.9*	54.6 $\pm$ 77.4	7.1 $\pm$ 3.0*	12.6 $\pm$ 3.7*
Significance of differences among otitis media types		<.01	<.01	NS	<.01	<.01

HPF — high-power field, NS — not statistically significant.

*Statistically different from control group ($p < .05$).

trols, but not when those in the acute late stage were compared with those in the subacute stage (Table 3). Fibroblastic density decreased in the acute early stage and increased in the subacute and chronic stages; however, these differences were not statistically significant. Capillary vasodilatation and vascularization were significantly increased in the acute late, subacute, and chronic stages when compared to the normal, but there were no statistically significant differences among the three stages of otitis media.

Blockage of the eustachian tube in cats produced otitis media that if left untreated led to all of the various stages of otitis media. Statistically significant changes were observed between nonadjacent stages, but not between adjacent stages. This statistical overlap between adjacent stages indicates a continuum of pathologic changes in otitis media.

Permeability of Round Window Membrane During Otitis Media. Studies of round window membrane permeability are important because of secondary damage to the inner ear that may result from middle ear disease. The outer epithelial layer of the round window membrane is contiguous with the mucoperiosteum of the middle ear space. We have shown previously that the histopathologic changes in the round window membrane in otitis media are similar to the changes observed in middle ear mucosa.¹² To evaluate changes in round window membrane permeability that might occur in otitis media, we examined the passage of an electron-dense tracer, horseradish peroxidase (HRP), through the round window membrane in cats with otitis media induced by eustachian tube obstruction.

Horseradish peroxidase was placed on the round window membranes of four nonobstructed cats, four cats whose tubes had been obstructed bilaterally for 3 days, three cats obstructed for 1 week, and five cats obstructed for 2 weeks following anesthesia with 30 mg/kg ketamine hydrochloride containing acepromazine. One animal was not used because it failed to develop a middle ear effusion. The HRP tracer was left on each round window membrane for a period of 2 minutes, and then the animal was

killed painlessly. The cochleas, including the round window membranes, were processed for electron microscopic evaluation.

Because the samples were perfused during processing, the presence of HRP within the scala tympani was not considered an indication of round window membrane permeability. Reaction products of HRP were counted only if they occurred within the layers of the round window membrane. Samples with artifactual disruption of the round window membrane were discarded. Round window membrane permeability was evaluated by the depth of tracer permeation (middle ear layer, fibrous layer, inner mesothelial layer). Permeability to HRP in both nonobstructed cats and cats with otitis media occurred by micropinocytosis.

The HRP tracer was observed within intercellular spaces, but was not observed within the tight junctions. The HRP was observed in the middle ear layer of the round window membrane in two normal (control) ears, in the fibrous layer in two control ears, and in the inner mesothelial layer in one control ear (Table 4). After 3 days of tubal obstruction, a clear effusion in the middle ear was observed in four ears from this group, and a thin purulent effusion in the fifth ear. Edema of the subepithelial spaces after 3 days of obstruction occurred in all ears except one, and infiltration of polymorphonuclear leukocytes was observed in the subepithelial space of the round window membrane of the ear with purulent effusion. After 3 days of obstruction, HRP was observed within the middle ear layer of the round window membrane in three ears, in the fibrous layer in one ear, and the inner layer in one ear.

TABLE 4. PERMEABILITY OF ROUND WINDOW MEMBRANE AS SHOWN BY NUMBER OF MEMBRANES WITH HORSERADISH PEROXIDASE AT EACH LAYER

Round Window Membrane Layer	Duration of Eustachian Tube Obstruction			
	0	3 Days	1 Week	2 Weeks
No passage	0	0	5	7
Middle ear layer	2	3	0	1
Fibrous layer	2	1	0	0
Inner layer	1	1	0	0
Total no. of ears	5	5	5	8

TABLE 5. SEMIQUANTITATIVE MEASUREMENTS OF PATHOLOGIC FINDINGS IN TENSOR TYMPANI MUSCLE IN OTITIS MEDIA

Type of Otitis Media	No. of Specimens	Fatty Infiltration	Inflammatory Change		
			Fibrosis	Fibroblasts	Inflammatory Cell Infiltration
None	27	1.0±0.5	0.3±0.4	0.2±0.4	0.0±0.0
Purulent	17	1.1±0.7	1.0±0.6	1.1±1.0	0.6±0.9
Serous	30	1.3±0.5	0.8±0.5	0.7±0.7	0.1±0.5
Chronic	31	2.0±0.6	1.7±0.8	1.3±1.0	0.5±0.8

Values represent mean±SD. Semiquantitative scoring system is indicated by 0 — no pathologic change, 1 — mild pathologic change, 2 — moderate pathologic change, 3 — severe pathologic change.

One week after obstruction, a thin purulent middle ear effusion was observed in four ears. There was edema of the subepithelial space of the round window membrane and a thickening of the membrane due to an infiltration of polymorphonuclear leukocytes. In this group, the tracer was not observed within any layer of the round window membrane.

Two weeks following obstruction of the eustachian tube, a thick, cloudy effusion and granulation tissue were observed within the middle ear cavity of all eight ears. These round window membranes were severely thickened and contained polypoidal invaginations. Granulation tissue filled the round window niche. The tracer did not enter into any layer of the round window membrane in seven ears and entered one cell of the middle ear layer in one ear.

Permeability to HRP after 1 to 2 weeks of tubal obstruction was considerably reduced compared with that in normal cats or in cats that had 3 days of obstruction. We believe that this reduction in permeability was due to 1) protection afforded by residual effusion overlying the round window membrane, 2) thickening of the round window membrane due to inflammatory cell infiltration of the subepithelial space, and 3) presence of granulation tissue within the round window niche.

HUMAN MORPHOMETRY

Thickness of Human Round Window Membrane in Different Forms of Otitis Media. A total of 37 normal human temporal bones, 23 temporal bones with serous otitis media (SOM), 34 with purulent otitis media (POM), and 55 with chronic otitis media (COM) from six age groups (birth to 12 months,

13 months to 5 years, 6 to 12 years, 13 to 30 years, 31 to 60 years, and 60 years and older) were selected from the University of Minnesota Temporal Bone Bank for a study of round window membrane thickness. We reasoned that otitis media would affect membrane thickness in humans as in cats, thereby altering its ability to act as a barrier between middle and inner ear.

Cross sections of the round window membranes where the niche and the membrane were at their widest were selected for measurement by use of a calibrated eyepiece micrometer set at a magnification of 100x. Membrane thickness was measured at the midpoint of the distance between the tips of the crest of the cochlear fenestra, and at two points 0.2 mm from either side of that midpoint. Mean thicknesses and standard deviations were calculated from these three measurements. The 95% confidence interval of the group means was used to compare group differences.

Thickness did not differ significantly among age groups in temporal bones from the normal group or from groups with SOM, POM, or COM. However, mean thickness in specimens with SOM (0.089 ± 0.007 mm), POM (0.096 ± 0.022 mm), and COM (0.114 ± 0.114 mm) was significantly greater than in normal specimens (0.069 ± 0.004 mm). Thickness in COM was significantly greater than in either SOM or POM. We conclude that thickness of the round window membrane does not increase with age, ie, that the membrane is fully mature at birth and that thickness increases during otitis media, especially in COM.

Tensor Tympani in Different Forms of Otitis Media. It is our hypothesis that irritation or inflammation of the tensor tympani muscle and tendon leads

TABLE 6. QUANTITATIVE MEASUREMENTS OF DIAMETER IN TENSOR TYMPANI MUSCLE IN OTITIS MEDIA

Type of Otitis Media	No. of Specimens	Muscle (μ m)	Tendon (μ m)	Largest Fiber (μ m)	Smallest Fiber (μ m)	Frequent Fiber (μ m)
None	27	1,194.4±284.4	357.4± 62.7	19.1±6.8	7.3±3.0	12.7±4.9
Purulent	17	1,323.5±242.2	408.8± 87.4*	15.6±3.7*	6.2±1.8	10.2±4.0*
Serous	30	1,437.5±281.9	426.6± 87.8*	14.8±4.1*	6.6±2.0	10.3±3.7
Chronic	31	1,459.6±252.8*	492.5±110.0*†	14.0±4.6*	5.3±1.6*	9.4±3.9*

Values represent mean diameter±SD.

*Significant difference between groups with otitis media and group with none ($p < .05$).

†Significant difference between groups with various types of otitis media ($p < .05$).

TABLE 7. QUANTITATIVE MEASUREMENTS OF NUMBER OF FIBERS AND NUCLEI IN TENSOR TYMPANI MUSCLE IN OTITIS MEDIA

Type of Otitis Media	No. of Specimens	Normal Fibers	Normal Nuclei	Abnormal Fibers	Abnormal Nuclei
None	27	11.3±3.5	84.2±31.6	0.2±0.6	5.7± 5.3
Purulent	17	11.1±2.7	89.2±37.6	1.0±1.4	13.7±14.9
Serous	30	8.6±3.3*	56.7±33.4*	1.8±2.1*	18.4±17.9*
Chronic	31	8.1±4.2	45.5±33.4*	2.0±2.5*	23.0±14.8*

Value represent mean±SD.

*Significant difference between groups with otitis media and group with none ($p < .05$).

to spasm or contraction of the muscle resulting in retraction and fixation of the tympanic membrane and ossicles. We examined 105 human temporal bones: 27 from ears without otitis media, 17 with POM, 30 with SOM, and 31 with COM. Medical histories from these patients revealed no congenital anomalies, malignancies, leukemias, myopathies, septicemias, bacteremias, or general pathologic or metabolic diseases affecting the musculoskeletal system.

Semiquantitative measurements included evaluation of inflammatory changes, such as fibroblastic reaction and inflammatory cells, and evaluation of atrophic or degenerative changes, such as fatty infiltration. Severity of change was graded (0 = none, 1 = mild, 2 = moderate, and 3 = severe), and results were analyzed by the χ^2 method.

Quantitative measurements included 1) the diameter of the tensor tympani muscle, taken as the cross-diameter of the muscle between the apical turn of the cochlea and the apex of the supratubal recess; 2) the diameter of the tensor tympani tendon, taken as the widest diameter in the midpoint between the lateral attachment to the malleus and the base of the cochleariform process; 3) the largest, smallest, and the most frequent muscle fiber diameters; 4) the number of normal muscle fibers and nuclei per high-power field; and 5) the number of abnormal muscle fibers and nuclei per high-power field. Quantitative results were assessed by analysis of variance (Duncan's multiple-range test).

Densities of fibrosis and fibroblasts were greater in groups with otitis media of any kind than in the group without otitis media (Table 5). Densities were also greater in specimens with COM than in those with SOM or POM. Inflammatory cell infiltration was greater in groups with COM and POM than in specimens without otitis media or with SOM. Fatty cell infiltration was seen to increase with increasing age. The increase was greater in the groups with otitis media than in those without otitis media.

Numbers of normal muscle fibers and normal nuclei decreased and numbers of abnormal fibers and abnormal nuclei increased to a greater degree in COM than in SOM or POM (Tables 6 and 7). The changes were more severe in all categories of otitis media than in specimens without otitis media. The

diameter of the tensor tympani muscle and tendon increased progressively from POM to SOM and to COM. Diameters of individual muscle fibers, however, were smaller in groups with otitis media than in those without otitis media, and smaller in those with COM than in those with SOM or POM. Statistical analysis showed no relationship between time elapsed between death and fixation and the type of atrophic and degenerative muscle changes.

We conclude that pathologic changes in the tensor tympani muscle and tendon are more severe in temporal bones with SOM and POM than temporal bones without otitis media, and that changes in COM are of even greater severity.

DISCUSSION

It is our understanding that the middle ear, like any other organ, reacts to an injurious agent with a typical inflammatory response. The different types of middle ear effusion and the clinical manifestations with which they are associated represent this inflammatory response. Regardless of the nature of the insult, a series of events will be triggered within the middle ear cleft, and early vascular and exudative phases will lead, if the insult persists, to a later proliferative (fibroblastic) phase. Although there is probably no single etiologic factor in otitis media, compromise of the eustachian tube through either obstruction or dysfunction is generally considered a common factor associated with otitis media.

Employing an animal model studied under controlled conditions, we have presented evidence that changes in the mucosa of the middle ear in otitis media due to obstruction of the eustachian tube occur along a continuum, with early forms of otitis media leading to chronic disease. Using this same model, we demonstrated an increase in the thickness and a decrease in the permeability of the round window membrane, both of which progressed with the duration of the obstruction.

The study of human temporal bones revealed histopathologic changes in otitis media with effusion and in COM that were remarkably similar to changes seen in the animal model. In humans as in cats, thickness of the round window membrane increased with disease severity. Histopathologic changes in the tensor tympani muscle and tendon followed the same pattern and were more severe in the chronic stage of otitis media than in the serous or

purulent stages. These results support the concept that all cases of otitis media represent different

stages of a continuum of events in middle ear inflammation.

REFERENCES

1. Paparella MM, Hiraide F, Juhn SK, Kaneko Y. Cellular events involved in middle ear fluid production. *Ann Otol Rhinol Laryngol* 1970;79:766-79.
2. Hiraide F, Paparella MM. Vascular changes in middle ear effusions. *Arch Otolaryngol* 1972;96:45-51.
3. Juhn SK, Paparella MM, Kim CS, Goycoolea MV, Giebink GS. Pathogenesis of otitis media. *Ann Otol Rhinol Laryngol* 1977;86:481-92.
4. Goycoolea MV, Paparella MM, Carpenter A-M. A longitudinal study of cellular changes in experimental otitis media. *Otolaryngol Head Neck Surg* 1979;87:685-700.
5. Goycoolea MV, Paparella MM, Carpenter A-M. Infiltration of the tensor tympani and stapedius muscles in otitis media. An experimental study in the cat. *Int J Pediatr Otorhinolaryngol* 1979;1:231-9.
6. Bak-Pedersen K, Tos M. Mucous glands in the middle ear and osseous eustachian tube. *Ann Otol Rhinol Laryngol* 1973;82:80-8.
7. Bak-Pedersen K, Tos M. Distribution and density of goblet cells in the normal adult human middle ear. *Ann Otol Rhinol Laryngol* 1973;82:240-7.
8. Tos M. Experimental tubal obstruction. Changes in middle ear mucosa elucidated by quantitative histology. *Acta Otolaryngol (Stockh)* 1981;92:52-61.
9. Paparella MM, Sipilä P, Juhn SK, Jung TK. Subepithelial space in otitis media. *Laryngoscope* 1985;95:414-20.
10. Okazaki N, DeMaria TF, Briggs BR, Lim DJ. Experimental otitis media with effusion induced by nonviable *Hemophilus influenzae*. *Am J Otol* 1984;5:80-92.
11. Modified Report of the Ad Hoc Committee on Definition and Classification of Otitis Media. *Ann Otol Rhinol Laryngol* 1980;89(suppl 69):6-8.
12. Goycoolea MV, Paparella MM, Carpenter A-M, Juhn SK. Oval and round window changes in otitis media: an experimental study in the cat. *Surg Forum* 1978;29:578-80.

MORPHOMETRIC STUDIES OF THE CONTINUUM OF OTITIS MEDIA

TAE H. YOON, MD
PATRICIA A. SCHACHERN

MICHAEL M. PAPARELLA, MD
BRUCE R. LINDGREN, MS

MINNEAPOLIS, MINNESOTA

Morphometric changes in the epithelium and subepithelium of the middle ear mucosa from children younger than 10 years of age were measured at the promontory in 85 temporal bones with otitis media and in 29 normal temporal bones by use of quantitative and semi-quantitative methods. Comparisons of morphologic analysis in different otitis media types showed that acute inflammatory changes were usually seen in purulent otitis media with effusion and serous otitis media with effusion, and chronic inflammatory changes were more severe in mucoid otitis media with effusion and chronic otitis media. There were overlaps, however, in histopathologic findings between different types of otitis media that suggest a continuum of otitis media types, with one type of otitis media changing into another type.

KEY WORDS — continuum, morphometry, otitis media, temporal bone.

INTRODUCTION

Otitis media, an inflammation of the middle ear cleft, was classified into different types based on characteristics of middle ear effusion (MEE) and evidence of irreversible pathologic changes by Paparella¹ and later modified by an ad hoc committee report.² Middle ear effusion is categorized into three basic types: serous, purulent, and mucoid.² A high incidence of persistent MEE has been observed in young children.³⁻⁵ It has been suggested that all cases of otitis media represent different stages of a continuum of events that can result in irreversible pathologic changes.^{1,6} Although the continuum of events has been documented in animal models of induced otitis media,^{7,8} it is difficult to evaluate the continuum of changes in human temporal bones. In a previous study of human temporal bones, a continuum of changes in the subepithelial space of the middle ear mucosa in different types of otitis media has been suggested.⁹

The aim of this study was to compare morphologic changes in the epithelium and subepithelial space in different otitis media types in human temporal bones, concentrating on morphometric changes in middle ear mucosa from children younger than 10 years of age. Quantitative and semiquantitative measurements taken from a designated portion of the promontory were used.

MATERIALS AND METHODS

Two hundred fifty-one human temporal bones from 129 children younger than 10 years of age were reviewed for MEE or irreversible pathologic changes. All specimens were processed by fixation, decalcification, and celloidin-embedding techniques. Each section was cut at a thickness of 20 μ m, and every 10th section was stained with hematoxylin and eosin. After excluding temporal bones with in-

significant otitis media and bones from patients with systemic disease, a total of 114 temporal bones were available for study, which included 85 temporal bones with otitis media from 51 children and 29 normal temporal bones without any effusion or inflammatory changes from 21 children. Excluded were bones with only scant effusion confined to a localized area of the middle ear cleft, as this was considered to represent insignificant otitis media. Specimens from patients with systemic diseases such as leukemia and lymphoma were excluded because of cellular infiltration in the middle ear cavity and mucoperiosteum.

The various otitis media types were classified according to MEE characteristics and presence of irreversible pathologic changes. Three types of effusion (serous, purulent, and mucoid) were categorized as previously defined.^{1,2} Since combinations of MEE types frequently were observed in different levels of the same temporal bones, these bones were classified by the predominant type of effusion. The presence of irreversible pathologic changes included granulation tissue, cholesterol granuloma, cholesteroloma, and ossicular erosion.¹⁰

Temporal bones with otitis media were categorized as otitis media with effusion (OME), which refers to temporal bones with MEE, without irreversible pathologic changes; and as chronic otitis media (COM), which refers to temporal bones containing irreversible pathologic changes primarily, with or without MEE. Temporal bones with OME were further categorized as serous otitis media with effusion (SOME), purulent otitis media with effusion (POME), and mucoid otitis media with effusion (MOME).

Morphometric measurements were made at three designated portions of the promontory at the level

From the University of Minnesota Otitis Media Research Center and the Department of Otolaryngology, University of Minnesota Medical School (Yoon, Paparella, Schachern); the Biostatistics Division, University of Minnesota School of Public Health (Lindgren); and the Minnesota Ear, Head and Neck Clinic (Paparella); Minneapolis, Minnesota. Supported in part by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant 8P50-DC-00133, the Deafness Research Foundation, and the International Hearing Foundation.

REPRINTS — Tae H. Yoon, MD, Minnesota Ear, Head and Neck Clinic, 701 25th Ave S, Minneapolis, MN 55454.

TABLE 1. TYPES OF MIDDLE EAR EFFUSION IN OTITIS MEDIA WITH EFFUSION AND CHRONIC OTITIS MEDIA

Disease Category	Serous		Purulent		Mucoid		Total
	No. of Ears	%	No. of Ears	%	No. of Ears	%	
Otitis media with effusion*	20	43	19	39	9	19	48
Chronic otitis media†	13	35	8	22	16	43	37

*Without irreversible pathologic changes.

†With irreversible pathologic changes.

of the hook end of the cochlea: one measurement at the center of that location, and two adjacent to the central portion at a distance of 250 μm — and their average was used in the analysis.

Quantitative measurements were made of 1) the thickness of the subepithelial space, measured in units of 25 μm ; 2) vascularization, measured as the number of vessels within a 100- μm length of the subepithelial space; and 3) vasodilatation, measured as the percentage of the number of vessels over 10 μm in diameter among the total number of vessels within a 100- μm length of subepithelial space.

Semiquantitative scores were calculated as follows: 1) type of lining epithelium: 1 = squamous cell; 2 = cuboidal cell; 3 = columnar cell; 2) density of ciliated cells or goblet cells, measured as the percentage of ciliated or goblet cells measured along a 100- μm length of epithelium: 0 = no cells; 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; 4 = 76% to 100%; 3) density of inflammatory cells or fibroblasts, measured as the number of cells per high-power field: 0 = no cells; 1 = 1 to 25 cells; 2 = 26 to 50 cells; 3 = 51 to 100 cells; 4 = 101 to 200 cells; 5 = 201 to 400 cells; 6 = over 401 cells; and 4) density of polymorphonuclear leukocytes (PMNs), measured as the percentage of PMNs among the total numbers of inflammatory cells: 0 = no cells; 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; 4 = 76% to 100%.

Analysis of variance was used to test statistical significance of the accumulated measurements among groups. Means of all samples were compared simultaneously by the F test. If a significant F ($p < .05$) was obtained, the 95% confidence interval was employed to test which means were significantly different. A significant difference between group means was taken as an absence of overlap of 95% confidence intervals.

RESULTS

The 85 temporal bones with otitis media were divided into groups: 48 with OME and 37 with COM (Table 1). Serous or purulent effusion was frequent in OME, and mucoid effusion was most frequent in COM (χ^2 test, $p < .05$).

Epithelial Changes. The epithelial lining cells of

TABLE 2. EPITHELIAL CHANGES IN OTITIS MEDIA WITH EFFUSION AND CHRONIC OTITIS MEDIA

Disease Category	No. of Ears	Lining Cells	Ciliated Cells	Goblet Cells
Normal	29	1.16 $\pm$ 0.14	0.27 $\pm$ 0.32	0
OME	48	2.02 $\pm$ 0.68*	1.48 $\pm$ 1.24*	0.35 $\pm$ 0.52*
COM	37	2.39 $\pm$ 0.61*	1.94 $\pm$ 1.26*	0.71 $\pm$ 1.00*

OME vs COM

NSD

NSD

NSD

For scoring system (scores are given as mean $\pm$ SD), see text.

OME — otitis media with effusion, COM — chronic otitis media, NSD — no significant difference between OME and COM.

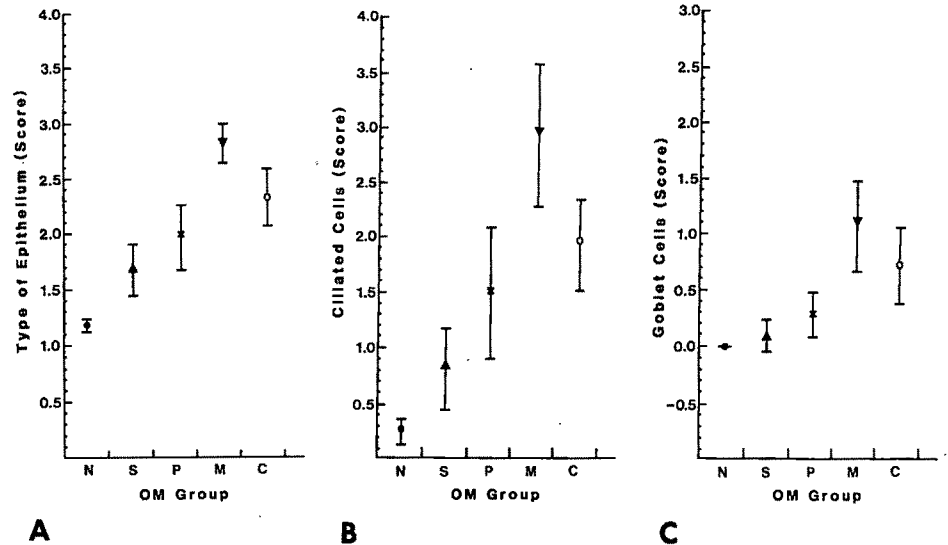
*Statistically different from normal ($p < .01$).

the normal middle ear at the promontory usually consisted of squamous or cuboidal nonciliated cells. Ciliated cells were occasionally observed at this location, but goblet cells were not. The epithelial lining of the promontory in OME consisted of cuboidal cells and in COM consisted of cuboidal-to-columnar cells. The mean scores of lining cells, ciliated cells, and goblet cells were increased in otitis media (Table 2). The increase in epithelial changes was more severe in COM than in OME, but the difference between these two groups was not statistically significant.

Changes in the type of epithelial lining were observed in all types of otitis media. Epithelial metaplasia was most frequent in MOME, and less prevalent in SOME and POME (Fig 1A). Squamous-to-cuboidal cells were mostly observed in SOME, cuboidal cells in POME, and cuboidal-to-columnar cells in MOME and COM. Epithelial metaplasia in MOME was significantly greater than in SOME, POME, or COM, but there were overlaps of 95% confidence intervals between SOME and POME and between POME and COM indicating absence of significant differences between these categories. The mean density of ciliated cells was significantly increased in all types of otitis media, but was greatest in MOME (Fig 1B). There were overlaps of 95% confidence intervals between MOME and COM, COM and POME, and POME and SOME. The mean goblet cell density was greatest in MOME, and less in COM and POME (Fig 1C). Although there was a slight increase in number of goblet cells in SOME, it was not significant when compared with numbers in normal ears. There were overlaps of 95% confidence intervals between MOME and COM, COM and POME, and POME and SOME.

Subepithelial Changes. Histopathologic measurements of subepithelial changes are listed in Table 3. The mean thickness of the subepithelial layer of the normal middle ear at the promontory was 37.5 μm (SD = 12.5 μm). The mean density of inflammatory cells was less than 25 cells per high-power field and the mean density of fibroblasts was 51 to 100 cells per high-power field. Polymorphonuclear leukocytes were not observed in normal submucosa. The mean number of vessels within a 100- μm length of subepithelial space was two, and the mean propor-

Fig 1. Epithelial changes in various types of otitis media. For scoring system, see text. Values are expressed as means and 95% confidence intervals in each group. N — normal group (29 ears), S — serous otitis media with effusion (20 ears), P — purulent otitis media with effusion (19 ears), M — mucoid otitis media with effusion (9 ears), C — chronic otitis media (37 ears). A) Type of lining epithelial cells. B) Density of ciliated cells. C) Density of goblet cells.



tion of vasodilatation was 12.8%. Large amounts of mesenchyme were not observed at the promontory.

In temporal bones with otitis media, increases in thickness and vascularization were more severe in COM than in OME. Increased vasodilatation, however, was significant only in OME, and the increased density of fibroblasts was significant only in COM when compared with normal. Although the density of inflammatory cells was more increased in COM than in OME, and the percentage of PMNs was more increased in OME than in COM, these differences were not statistically significant.

A significant increase in thickness of the subepithelial space was observed in all types of otitis media (Fig 2A). There was a stepwise increase in thickness from normal to SOME, POME, MOME, and COM, respectively. However, there were overlaps of 95% confidence intervals among groups with each type of otitis media, an exception being between COM and SOME. An increase in density of inflammatory cells was observed in SOME, COM, MOME, and POME in increasing order compared with normal ears (Fig 2B). However, overlaps of 95% confidence intervals were seen among POME, MOME, and COM. The most severe increase in PMN density was seen in POME (Fig 2C).

A slightly decreased fibroblast density was observed in SOME, a slightly increased density in

POME, and a markedly increased density in MOME and COM (Fig 2D). Overlaps were observed between COM and MOME.

Although vascularization was increased in all types of otitis media compared to normal, a significant increase was seen in SOME, POME, and COM in increasing order (Fig 2E). There were overlaps of 95% confidence intervals among groups with each type of otitis media, the exception being between COM and SOME. A significant increase in vasodilatation compared to normal was seen only in POME and SOME (Fig 2F). There were overlaps of 95% confidence intervals between POME and SOME, SOME and MOME, and MOME, COM, and normal.

DISCUSSION

This study of temporal bones from children with COM revealed that chronic MEEs were frequently associated with irreversible pathologic changes, and mucoid effusions were the most frequently associated type, suggesting that mucoid effusion develops from long-standing otitis media. Clinically, in MOME, the history is often of inflammation of longer duration than in SOME or POME. Mucoid effusion has been observed frequently in young children having a diagnosis of COM.¹¹

Similarly, the continuum of events, from serous

TABLE 3. SUBEPITHELIAL CHANGES IN OTITIS MEDIA WITH EFFUSION AND CHRONIC OTITIS MEDIA

Disease Category	No. of Ears	Thickness	Inflammatory Cells	PMNs	Fibroblasts	Vascularization	Vasodilatation
Normal	29	1.50 ± 0.50	0.87 ± 0.46	0 ± 0	2.41 ± 0.45	2.00 ± 0.72	12.08 ± 10.30
OME	48	3.92 ± 2.54*	2.62 ± 1.48*	0.66 ± 0.93*	2.79 ± 0.75	4.07 ± 2.20*	27.66 ± 11.33*
COM	37	6.35 ± 4.02*	2.70 ± 1.44*	0.24 ± 0.49*	3.47 ± 0.67*	6.43 ± 4.34*	18.22 ± 11.22
OME vs COM		SD	NSD	NSD	SD	SD	SD

For scoring system (scores are given as mean ± SD), see text.

PMNs — polymorphonuclear leukocytes, OME — otitis media with effusion, COM — chronic otitis media, SD — significant difference between OME and COM ($p < .05$), NSD — no significant difference between OME and COM.

*Statistically different from normal ($p < .01$).

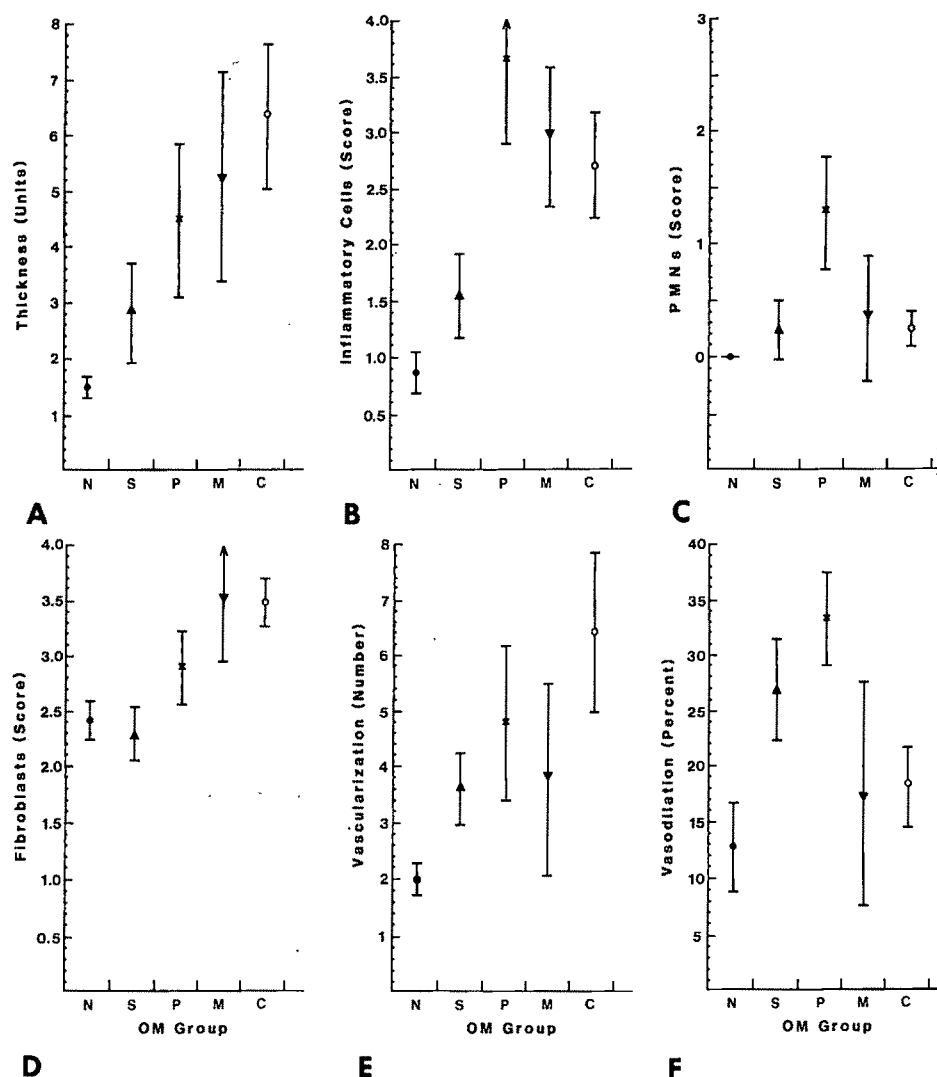


Fig 2. Subepithelial changes in various types of otitis media. For scoring system, see text. Values are expressed as means and 95% confidence intervals in each group. N — normal group (29 ears), S — serous otitis media with effusion (20 ears), P — purulent otitis media with effusion (19 ears), M — mucoid otitis media with effusion (9 ears), C — chronic otitis media (37 ears). A) Thickness (units). B) Density of inflammatory cells. C) Density of polymorphonuclear leukocytes (PMNs). D) Density of fibroblasts. E) Vascularization (number of vessels). F) Vasodilation (percentage).

or purulent effusion to mucoid effusion and, finally, to chronic pathologic conditions or sequelae, has been observed in animals with experimental otitis media.^{7,8} Whereas the term "chronic" has been suggested for an inflammation lasting at least 8 weeks in humans,² this term may not apply in a histopathologic study of human temporal bones, since granulation tissue in the middle ear cleft has been reported to occur prior to 8 weeks in animal studies.¹²

In the present study, residual mesenchyme in various degrees was commonly observed in the middle ear, but significant amounts of mesenchyme were not present at the promontory in normal children. These results agree with those of a previous study in which mesenchyme was observed to resolve most rapidly at the promontory.¹³ In our study of the epithelial lining of the promontory in the normal middle ear, the major cells found were squamous or cuboidal cells, with some variations of ciliated cells. The presence of ciliated cells at the promontory has been previously reported in normal middle ear mucosa.^{14,15} Although it has been reported that goblet cells are irregularly scattered at the

promontory,^{16,17} we did not confirm these findings in our selected portion of the promontory. In general, epithelial metaplasias occur more frequently in COM than in OME, but we observed more frequent changes in the epithelium in MOME than in COM.

An increased thickness of the subepithelial space was commonly observed in all types of otitis media. This increased thickness may be due to acute inflammatory changes, such as edema, vasodilatation, and infiltration of PMNs in POME, and to edema and vasodilatation in SOME. Edematous subepithelial widening in SOME and POME has been reported.⁷⁻⁹ Most of the histopathologic findings seen in MOME were similar to those seen in COM. A remarkable increase in thickness of the subepithelial space was observed in COM and MOME. The increased thickness in MOME is related to an increased density of fibroblasts and inflammatory cells, and in COM it is related to an increased density of fibroblasts, inflammatory cells, and vascularization. Proliferation of fibroblasts was reported in MOME and COM.⁷⁻⁹ The formation of granulation tissue, consisting of fibroblasts, inflam-

matory cells, and new blood vessels, was commonly observed in COM.^{9,10}

In summary, human temporal bone histopathology reveals that epithelial and subepithelial layers of the middle ear mucoperiosteum are actively involved in all stages of otitis media. Acute inflammatory changes are usually seen in POME and SOME,

while chronic inflammatory changes are more severe in MOME and COM. There are overlaps, however, in histopathologic findings between different types of otitis media that suggest a continuum of otitis media types, with one type of otitis media changing to another type. It appears that POME or SOME can change to MOME, which can change to COM.

REFERENCES

1. Paparella MM. Middle ear effusions: definitions and terminology. *Ann Otol Rhinol Laryngol* 1976;85(suppl 25):8-11.
2. Modified Report of the Ad Hoc Committee on Definition and Classification of Otitis Media. *Ann Otol Rhinol Laryngol* 1980;89(suppl 69):6-8.
3. Howie VM, Ploussard JH, Sloyer J. The otitis prone condition. *Am J Dis Child* 1975;129:676-8.
4. Shurin PA, Pelton SI, Donner A, et al. Persistence of middle ear effusion in children. *N Engl J Med* 1979;300:1121-3.
5. Teele DW, Klein JO, Rosner BA. Epidemiology of otitis media in children. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):5-6.
6. Paparella MM, Hiraide F, Juhn SK, Kaneko Y. Cellular events involved in middle ear fluid production. *Ann Otol Rhinol Laryngol* 1970;79:766-79.
7. Juhn SK, Paparella MM, Kim CS, Goycoolea MV, Giebink GS. Pathogenesis of otitis media. *Ann Otol Rhinol Laryngol* 1977;86:481-92.
8. Goycoolea MV, Paparella MM, Carpenter A-M, Juhn SK. A longitudinal study of cellular changes in experimental otitis media. *Otolaryngol Head Neck Surg* 1979;87:685-700.
9. Paparella MM, Sipilä P, Juhn SK, Jung TTK. Subepithelial space in otitis media. *Laryngoscope* 1985;95:414-20.
10. Meyerhoff WL, Kim CS, Paparella MM. Pathology of chronic otitis media. *Ann Otol Rhinol Laryngol* 1978;87:749-60.
11. Giebink GS, Le CT, Paparella MM. Epidemiology of otitis media with effusion in children. *Arch Otolaryngol* 1982;108:563-6.
12. Paparella MM, Schachern PA, Shea DA. Genesis of granulation tissue in animals. In: Sadé J, ed. Cholesteatoma and mastoid surgery. Proceedings of the Second International Conference. Amsterdam, the Netherlands: Kugler, 1982:181-9.
13. Takahara T, Sando I, Hashida T, Shibahara Y. Mesenchyme remaining in human temporal bones. *Otolaryngol Head Neck Surg* 1986;95:349-57.
14. Kawabata I, Paparella MM. Ultrastructure of normal human middle ear mucosa. Preliminary report. *Ann Otol Rhinol Laryngol* 1969;78:125-37.
15. Shimada T, Lim DJ. Distribution of ciliated cells in the human middle ear. Electron and light microscopic observations. *Ann Otol Rhinol Laryngol* 1972;81:203-11.
16. Lim DJ, Shimada T, Yoder M. Distribution of mucus-secreting cells in normal middle ear mucosa. *Arch Otolaryngol* 1973;98:2-9.
17. Tos M, Bak-Pedersen K. Goblet cell population in the normal middle ear and eustachian tube of children and adults. *Ann Otol Rhinol Laryngol* 1976;85(suppl 25):44-50.

EFFECT OF PROSTAGLANDIN, LEUKOTRIENE, AND ARACHIDONIC ACID ON EXPERIMENTAL OTITIS MEDIA WITH EFFUSION IN CHINCHILLAS

TIMOTHY T. K. JUNG, MD, PHD

LOMA LINDA, CALIFORNIA

YOUNG MIN PARK, MD

LOMA LINDA, CALIFORNIA

STANLEY MILLER

LOMA LINDA, CALIFORNIA

DANIEL SCHLUND, MD

LOMA LINDA, CALIFORNIA

ON WONG, MD

LOMA LINDA, CALIFORNIA

DOUGLAS WEEKS, MD

LOMA LINDA, CALIFORNIA

STEVEN K. JUHN, MD

MINNEAPOLIS, MINNESOTA

Although previous studies have shown that prostaglandins (PGs), leukotrienes (LTs), and other arachidonic acid (AA) metabolites play an important role in the pathogenesis of otitis media with effusion (OME), the exact role of each AA metabolite in OME is still unknown. The purpose of this study was to examine the effect of several individual AA metabolites alone or in combination and AA itself on experimental otitis media in chinchillas. Normal chinchillas were inoculated daily with normal saline, PGE₂, LTC₄, LTC₄ + PGE₂, and AA through the superior bullae over 7 days. Animals were followed by otoscopy and tympanometry, samples of middle ear effusion were collected for biochemical assay, and temporal bones were processed for histopathology. The highest number of ears that developed OME was in the group inoculated with PGE₂ + LTC₄. The degree of inflammatory change was more pronounced in groups injected with LTC₄ than any other group. The findings of this study suggest that eicosanoids PGE₂, LTC₄, and AA alone or in combination inoculated into the middle ear can induce OME.

KEY WORDS — animal model of otitis media, arachidonic acid, leukotrienes, otitis media, prostaglandins.

INTRODUCTION

Secretion of inflammatory mediators in the middle ear (ME) during infection or eustachian tube dysfunction causes increased vascular permeability and stimulates epithelial secretory activity, resulting in ME inflammation and effusion. Among the inflammatory mediators in otitis media (OM), prostaglandins (PGs), leukotrienes (LTs), and other arachidonic acid (AA) metabolites (eicosanoids) seem to play an important role in mediating inflammation. Evidence of the involvement of PGs, LTs, and other eicosanoids in the pathogenesis of OM includes 1) presence of PGs, LTs, and other eicosanoids in human middle ear effusion (MEE), 2) presence of AA metabolites in the MEE from animal models of OM, and 3) effectiveness of inhibitors of AA metabolism on the outcome of experimental OM.¹ An earlier study suggested that lipoxygenase products, such as LTs, may induce more ME inflammation than cyclooxygenase products, such as PGs, since treatment with nonsteroidal anti-inflammatory drugs seemed to worsen the inflammatory changes in experimental purulent OM.

In a comparative study of temporal bone histopathology of OM animal models, we demonstrated that MEs inoculated with AA showed more inflammatory reaction in the ME mucoperiosteum than

PGE₂-inoculated ears. This was explained by the fact that AA is converted to lipoxygenase products, which can induce more inflammatory changes than PGE₂ alone. However, it is not clear whether these products of AA metabolism alone can cause ME inflammation and effusion. Also, the histopathologic effect of each AA metabolite on the ME mucoperiosteum is not understood. The present study examined the effect of several individual AA metabolites alone and in combination and of AA itself on MEE biochemistry and histopathologic changes by use of the chinchilla OM model.

MATERIALS AND METHODS

Induction of Otitis Media. Twenty-four healthy chinchillas, each weighing approximately 500 g, were divided into the following six groups: saline control, PGE₂, LTC₄, PGE₂ + LTC₄, and AA in two different dosing schedules (AA-I and AA-II; Table 1). Under ketamine hydrochloride anesthesia (30 mg/kg, intramuscularly), daily inoculations of the experimental substance were given through bilateral superior bullae for 7 days. At the time of each inoculation, an air-venting needle was inserted into the superior bullae to prevent excessive pressure buildup. Otoscopy and tympanometry were performed on days 1, 3, 5, and 8, just before

From the Division of Otolaryngology-Head & Neck Surgery, Department of Surgery (Jung, Park, Schlund, Miller, Wong), and the Department of Pathology (Weeks), Loma Linda University School of Medicine and Jerry Pettis Memorial Veterans Hospital, Loma Linda, California, and the Department of Otolaryngology, University of Minnesota (Juhn), Minneapolis, Minnesota. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Loma Linda University School of Medicine.

REPRINTS — Timothy T. K. Jung, MD, PhD, Dept of Surgery, Loma Linda University Medical Center, Loma Linda, CA 92354.

TABLE 1. EXPERIMENTAL DESIGN
(N = 8 IN EACH GROUP)

Experimental Groups	Method of Testing
Saline control	Otoscopy
PGE ₂ 50 µg initially, 20 µg daily x6	Tympanometry
LTC ₄ 15 µg initially, 6 µg daily x6	Presence of fluid
PGE ₂ + LTC ₄ same dose as PGE ₂ and LTC ₄ , above	Lysozyme
AA-I 100 µg x1	High-performance liquid chromatography
AA-II 100 µg initially, 40 µg daily x6	Temporal bone histopatho- logic changes
PGE ₂ — prostaglandin E ₂ , LTC ₄ — leukotriene C ₄ , AA — arachi- donic acid.	

temporal bones were obtained. On day 8, animals were killed painlessly, samples of MEE were collected, and temporal bones were removed.

Lysozyme Assay. Concentrations of lysozyme in the samples of MEE were measured with a lysozyme test kit (Kallestad Co, Chaska, Minn).

MEE for AA Metabolites. The AA metabolites were extracted from MEE as previously described for radioimmunoassay of MEE.¹ The methanolic eluents containing AA metabolites were concentrated to 1 mL. One hundred microliters of the sample was injected into the high-performance liquid chromatography (HPLC) system and analyzed. The HPLC system (Shimadzu LC-6A) consisted of two pumps, a variable-wavelength UV detector (SPD-6A), and a C-18 reversed-phase column (Ultrasphere-ODS, 5 µm, 4.6 mm x 25 cm). A guard column (4.6 mm x 4 cm) was also packed with a C-18 reversed-phase column. The eluting solvent was 40% acetonitrile, 60% H₂O containing 0.1% acetic acid for cyclooxygenase products. The eluting solvent for lipoxigenase product was 70% methanol, 30% H₂O and 0.1% acetic acid, and 0.1% trifluoroacetic acid. The solvent was pumped isocratically at 1 mL/min for cyclooxygenase products and 1.5 mL/min for lipoxigenase products. Absorbance was monitored at 280 nm for the first 9 minutes, at 235 nm for the next 9 to 25 minutes, then at 280 nm for the next 25 to 32 minutes for lipoxigenase products, and at 195 nm for 12 minutes for cyclooxygenase products.

Temporal Bone Histopathology. On day 8, animals were perfused with 10% formalin solution through a catheter in the aorta. Temporal bones were removed, fixed in 10% formalin solution, decalcified in 5% trichloroacetic acid, dehydrated in a graded series of alcohols, embedded in paraffin, and sectioned to a thickness of 15 µm. Every 10th section was stained with hematoxylin and eosin for microscopic examination. To examine the same area from each temporal bone, a small section, approximately 1 cm in diameter, from the anterior-inferior aspect of the temporal bone was removed from each ear and processed by the same method as the entire bones. The presence of edema, hyper-

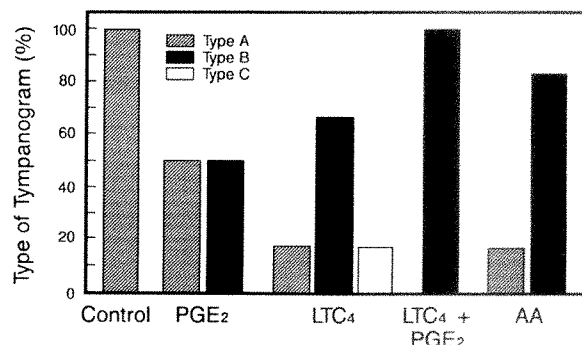


Fig 1. Tympanometric findings of experimental otitis media. Number of ears with type B tympanograms was highest in prostaglandin E₂ (PGE₂) plus leukotriene C₄ (LTC₄) group, followed by arachidonic acid (AA) group, LTC₄ group, PGE₂ group, and control group.

emia, leukocyte infiltration, focal hemorrhage, and osteoneogenesis was recorded.

RESULTS

Presence of MEE. Middle ear effusion was present in all six ears inoculated with PGE₂ + LTC₄, and in fewer ears inoculated with LTC₄ (5 of 6), AA (5 of 6), and PGE₂ (4 of 6). There was no fluid in the saline-inoculated control ears or the AA-I ears. The proportion of ears with type B tympanograms was highly correlated with the proportion of ears containing MEE (Fig 1).

Concentrations of Lysozyme. The mean concentrations of lysozyme in MEE were highest in the LTC₄ group (50.8 µg/mL), followed by the AA group (37.1 µg/mL), the PGE₂ group (23.5 µg/mL), and the PGE₂ + LTC₄ group (16.9 µg/mL) (Fig 2).

Concentrations of AA Metabolites. Results of the HPLC analysis of MEE for AA metabolites after injection with AA are shown in Fig 3. In the cyclooxygenase pathway, the metabolite with the highest concentration was thromboxane B₂, followed by 6-keto-PGF_{1α}, PGF_{2α}, PGD₂, and PGE₂. In the lipoxigenase pathway, the metabolite with the highest concentration was LTB₄, followed by LTC₄, 5-hydroxyeicosatetraenoic acid (HETE), and 15-

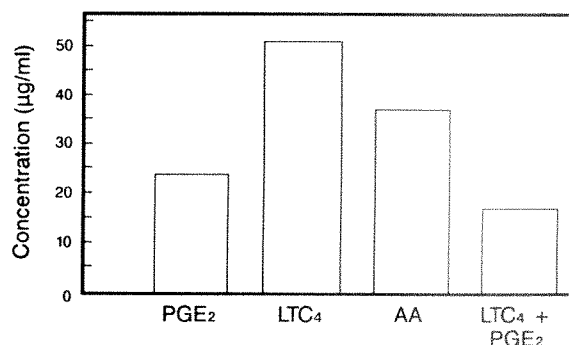


Fig 2. Lysozyme levels in middle ear effusion in each experimental group. Highest level was detected in leukotriene C₄ (LTC₄) group, followed by arachidonic acid (AA) group, prostaglandin E₂ (PGE₂) group, and PGE₂ + LTC₄ group.

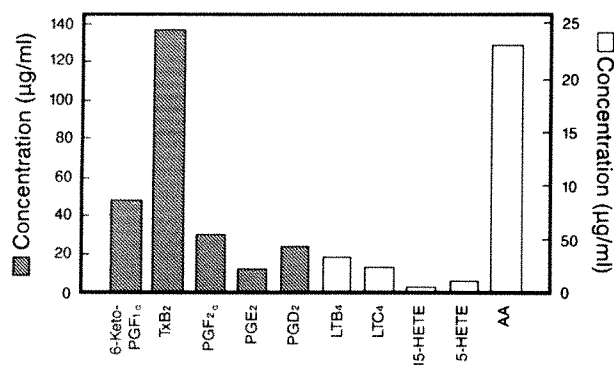


Fig 3. Results of high-performance liquid chromatography analysis and arachidonic acid (AA) metabolites in middle ear effusion after AA injections. PG — prostaglandin, Tx — thromboxane, LT — leukotriene, HETE — hydroxyicosatetraenoic acid.

HETE. The HPLC analyses of MEEs from other experimental groups also revealed more or less the same pattern.

Temporal Bone Histopathology. Some degree of ME mucoperiosteal inflammation was present in all experimental groups (Table 2). Inflammatory changes were most severe in ears inoculated with LTC₄, followed by the LTC₄ + PGE₂ group, the AA group, the PGE₂ group, and the control group (Fig 4).

All ears inoculated with LTC₄ and PGE₂ + LTC₄ showed edema and hyperemia (Fig 4). Experimental groups inoculated with PGE₂ and AA showed edema and hyperemia in 80% to 100% of the ears (Table 2). Edema and hyperemia were least frequent in the control group (33%).

Infiltration with polymorphonuclear leukocytes (PMNs) was most pronounced in the AA-II group and the LTC₄ group and was present in only 17% of the PGE₂ + LTC₄-inoculated ears (Fig 4). Few PMNs were seen in the AA-I group, the PGE₂ group, or the control group. Mononuclear leukocyte infiltration was seen most frequently in the LTC₄ group and the PGE₂ + LTC₄ group and was least frequent in the control group (Table 2 and Fig 4).

The degree of focal mucosal hemorrhage varied among the experimental groups (Fig 4). All ears in the LTC₄ and PGE₂ + LTC₄ groups, 60% of ears in the AA-II group, 50% of ears in the AA-I and PGE₂

groups, and 33% in the control group showed hemorrhage.

Osteoneogenesis was seen in 83% of the AA-I-inoculated group, in 50% of the PGE₂ + LTC₄ group, and in one of six control ears (Fig 4). There was no osteoneogenesis seen in the other groups.

DISCUSSION

This study demonstrates that inoculation of PGs, LTs, or AA into the ME of chinchillas without obstructed eustachian tubes can cause inflammation and effusion. Because of the short half-life of biologically active AA metabolites, and the patent eustachian tube, it was necessary to give daily inoculations rather than a single inoculation. Tympanometric findings correlated well with the presence of MEE. Prostaglandin E₂ and LTC₄ have a synergistic effect in inducing ME inflammation and effusion, since the group inoculated with PGE₂ + LTC₄ had the highest number of ears with effusion and type B tympanograms.

Others have suggested that PMNs and mononuclear leukocytes are principal sources of lysozyme levels in MEE during OM and that MEE lysozyme levels could be used as an index of inflammation in OM.² On the basis of MEE lysozyme levels in this study, LTC₄ inoculation produced the greatest inflammation; this finding could be explained by the extensive infiltration of PMNs and mononuclear leukocytes into the middle ear mucosa (MEM) observed in this group. The group inoculated with PGE₂ + LTC₄ had the lowest levels of lysozyme in the MEE; this finding could be explained by the fact that PGE₂ has both inflammatory and anti-inflammatory functions. Raud et al³ demonstrated that PGE₂ can suppress mediator release from mast cells in the hamster cheek pouch model.

Analysis of AA metabolites in MEE by HPLC after AA inoculation confirmed previous findings showing that MEM can convert AA into both cyclooxygenase and lipoxygenase products.⁴ It was surprising, however, to find a similar pattern of AA metabolites in MEE from other experimental groups, and we are presently validating these results by radioimmunoassay. Finding AA metabolites other than those inoculated might be explained

TABLE 2. PATHOLOGIC FINDINGS OF MIDDLE EAR MUCOSA

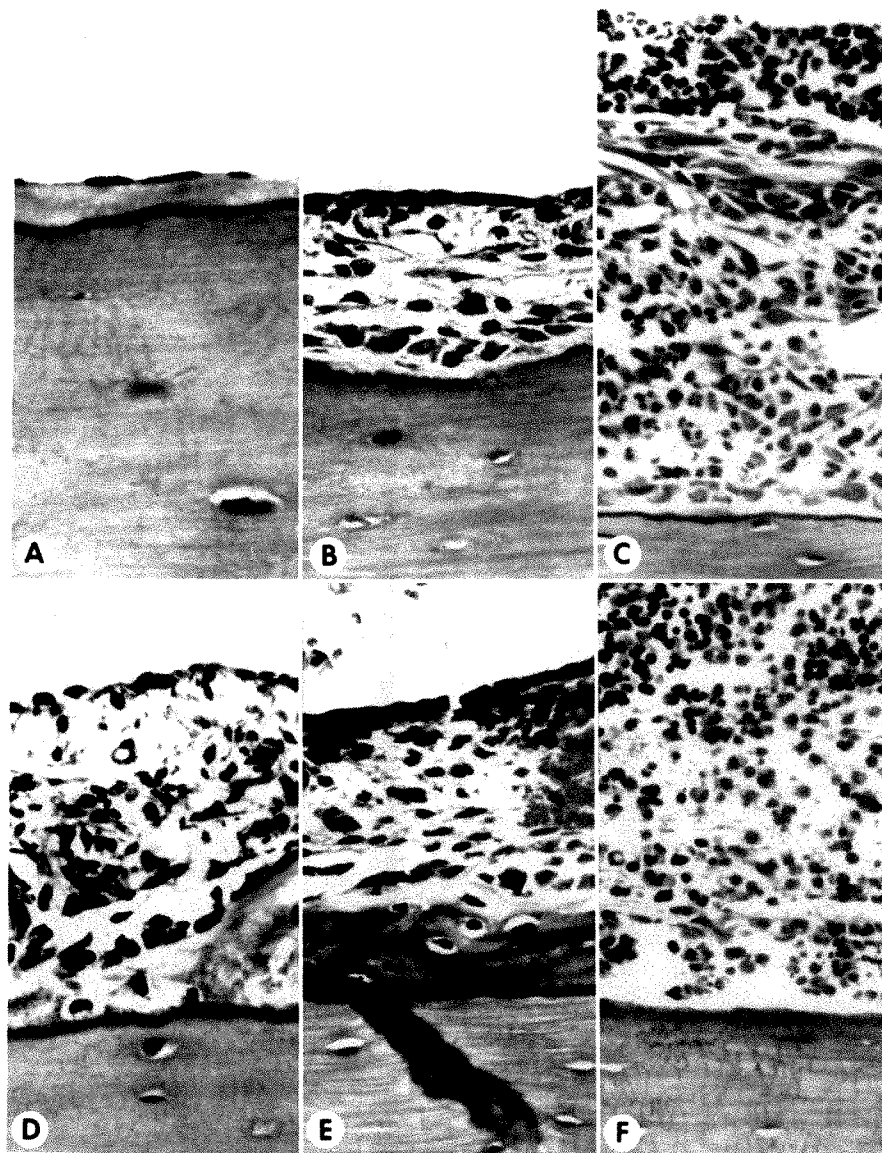
Experimental Group	Edema	Hyperemia	Leukocytes		Focal Hemorrhage	Osteoneogenesis
			PMN	Mono		
Control	33* (2/6)†	33 (2/6)	0 (0/6)	17 (1/6)	33 (2/6)	17 (1/6)
PGE ₂	83 (5/6)	83 (5/6)	0 (0/6)	67 (4/6)	50 (3/6)	0 (0/6)
LTC ₄	100 (4/4)	100 (4/4)	75 (3/4)	100 (4/4)	100 (4/4)	0 (0/4)
PGE ₂ + LTC ₄	100 (6/6)	100 (6/6)	17 (1/6)	100 (6/6)	100 (6/6)	50 (3/6)
AA-I	100 (6/6)	67 (4/6)	0 (0/6)	83 (5/6)	50 (3/6)	83 (5/6)
AA-II	80 (4/5)	80 (4/5)	80 (4/5)	80 (4/5)	60 (3/5)	0 (0/5)

PMN — polymorphonuclear, Mono — mononuclear. Other abbreviations as in Table 1.

*Percentage of ears studied in each group.

†Number of ears affected per number of ears studied.

Fig 4. Photomicrographs of chinchilla middle ear mucosa (original x100). A-C) Following serial inoculation of control and arachidonic acid (AA) metabolites. A) Saline control. B) Prostaglandin E2. C) Leukotriene C4. D-F) Following serial inoculation of AA metabolites and AA. D) Prostaglandin E2 plus leukotriene C4. E) AA in one injection. F) AA in seven injections.



by the fact that AA is actively metabolized by leukocytes and other cellular components in the MEM. Thus, AA metabolites found in the MEE samples in this study were derived both from exogenous inoculations and from *de novo* biosynthesis from the MEM itself. Therefore, the effect of PGE₂, LTC₄, and AA in the MEs observed in this study should be interpreted with care. Nevertheless, most of the effect observed probably resulted from the inoculated exogenous AA metabolites.

The ME mucoperiosteum from each experimental group showed some degree of inflammation. Edema and hyperemia can result from vasodilatation and increased vascular permeability due to PGs and LTs. Leukocyte infiltration was most pronounced in ears inoculated with LTC₄ and AA. Since high levels of highly chemotactic LTB₄ were detected in MEE samples from these groups, it was not surprising to find dense leukocyte infiltration. Focal hemorrhage was one of the most common fea-

tures in all experimental groups. Increased vascular permeability and vasodilatation due to PGs and LTs can mediate focal hemorrhage. Osteoneogenesis is a common feature seen in the histopathologic changes of animal models of OM.⁵ It is interesting to note that osteoneogenesis occurred only when both PGE₂ and LTC₄ were present. The significance of this observation is not clear.

Although it was impossible to identify a specific histopathologic response to each inflammatory mediator, certain histopathologic features of the MEM were associated with specific PG or LT inocula. For example, the MEM from the PGE₂ group was characterized by hyperemia, edema, and focal hemorrhage; the LTC₄ group by intense cellular infiltration, edema, focal hemorrhage, and hyperemia; the PGE₂ + LTC₄ group by edema, hyperemia, focal hemorrhage, cellular infiltration, and osteoneogenesis; and the AA group by edema, hyperemia, focal hemorrhage, cellular infiltration, and osteoneogen-

esis.

This study clearly showed that LTC₄ caused more inflammatory changes in the MEM than PGE₂. Leukotriene C₄ can induce MEE, since LTC₄ can mediate exudation of plasma.⁶ However, the addition of PGE₂ seemed to potentiate formation of MEE, since the highest number of ears developed effusion in the PGE₂ + LTC₄ group. On the other hand, the PGE₂ + LTC₄ group had lower lysozyme levels and less inflammatory change in the MEM compared to the LTC₄ group. This conflicting result may be explained by the dual effect (inflammatory and anti-

inflammatory) of PGE₂.

In summary, it is clear from this study that PGE₂, LTC₄, and AA alone and in combination are capable of inducing OM with effusion and ME inflammation. The PGE₂ + LTC₄ group had the highest number of ears with OM with effusion; this finding indicates potentiation of effusion by PGE₂. The LTC₄ group developed the most pronounced inflammatory changes in MEM. Prostaglandin E₂ also may have an anti-inflammatory effect in OM. Overall, LTC₄ in the ME caused more inflammation than PGE₂.

REFERENCES

1. Jung TTK. Prostaglandins, leukotrienes, and other arachidonic acid metabolites in the pathogenesis of otitis media. *Laryngoscope* 1988;98:980-93.
2. Juhn SK, Sipilä P, Jung TTK, Edlin J. Biochemical pathology of otitis media with effusion. *Acta Otolaryngol [Suppl] (Stockh)* 1984(suppl 414):45-51.
3. Raud J, Dahlen SE, Sydbom A, Linbom L, Hedquist P. Enhancement of acute allergic inflammation by indomethacin is reversed by prostaglandin E₂: apparent correlation with *in vivo* modulation of mediator release. *Proc Natl Acad Sci USA* 1988;85:2315-9.
4. Jung TTK, Juhn SK, Gerrard JM. Identification of prostaglandins and other arachidonic acid metabolites in experimental otitis media. *Prostaglandins Leukotrienes Med* 1982;8:249-61.
5. Jung TTK, Shea D, Giebink GS, Juhn SK. Comparative histopathology of animal models of otitis media in chinchillas: a temporal bone study. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. *Recent advances in otitis media with effusion*. Philadelphia, Pa: BC Decker, 1984:91-6.
6. Samuelsson B, Dahlen SE, Lindgren JA, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. *Science* 1987;237:1172-6.

ROLE OF MIDDLE EAR ENDOTOXIN IN INNER EAR INFLAMMATORY RESPONSE AND HYDROPS: LONG-TERM STUDY

DAVID J. LIM, MD

HIDEYUKI KAWAUCHI, MD

THOMAS F. DEMARIA, PHD

COLUMBUS, OHIO

The permeability of the round window membrane for *Salmonella typhimurium*-derived endotoxin was examined with use of a total of 33 chinchillas. One milligram of each endotoxin was instilled into the tympanic cavities via the superior bullae. The endotoxin activities in middle ear effusions (MEEs), perilymph, and sera were determined by limulus amoebocyte lysate assay. Endotoxin was detected in perilymph on the inoculated side by 12 hours after endotoxin instillation and persisted for up to 3 weeks. Endotoxin level peaked at 24 to 48 hours postinstillation, and it steadily declined afterward. This result suggests that the maximum penetration occurred during the active inflammatory stage. Histologic evidence demonstrated remarkable pathologic changes in the inner ear, including bleeding and inflammatory cell recruitment, mostly in the perilymphatic spaces (eg, scalae tympani, scalae vestibuli, spiral ligament), stria swelling, and sensory cell degeneration. This result suggests that endotoxin present in the middle ear can permeate the round window membrane, causing inner ear tissue damage in this animal model.

KEY WORDS — endotoxin, inner ear, otitis media, round window membrane.

INTRODUCTION

It has recently been demonstrated that there is transport of macromolecules, antibiotics, and bacterial toxins through the round window membrane between the middle and inner ear.¹⁻³ Bacterial endotoxins, which are potent pathogenic substances, have been found in middle ear effusions (MEEs) of patients with chronic otitis media with effusion.⁴⁻⁶ DeMaria et al⁷ demonstrated in an animal model that endotoxin derived from *Hemophilus influenzae*, which is a common otitis media pathogen, provokes severe inflammatory changes when it is inoculated into the tympanic cavity. In the present study, we evaluated the effects of endotoxin on the inner ear at various times after instilling endotoxin into the middle ear. We examined histologic evidence of disease in the cochlea and endolymphatic sac and compared this evidence with the endotoxin concentrations in the perilymph and middle ear.

MATERIALS AND METHODS

The middle ears of 33 chinchillas were injected with 1 mg of *Salmonella typhimurium*-derived endotoxin (1.27×10^7 endotoxin units [EU]) in 0.5 mL of sterile pyrogen-free saline. Bulla washes, perilymph, and serum samples were obtained at various times for up to 56 days postinjection and assayed for the presence of endotoxin by the quantitative chromogenic limulus amoebocyte lysate assay (Whittaker Bioproducts, Walkersville, Md), described in detail elsewhere.⁸ The temporal bones from 17 animals were processed for histologic evaluation by light microscopy as described previously.⁸

ENDOTOXIN LEVEL IN MIDDLE EAR EFFUSIONS AND PERILYMPH

The endotoxin levels in the perilymph and MEEs during the 56-day experimental period are shown in the Figure.

The mean endotoxin level in MEEs after endotoxin instillation was 1.8×10^7 EU/mL, and levels remained constant for the first 5 days of the experiment. Endotoxin concentrations in the perilymph showed considerable variability during the first 5 days of the experiment; values ranged from 0.53×10^7 to 0.8×10^7 EU/mL.

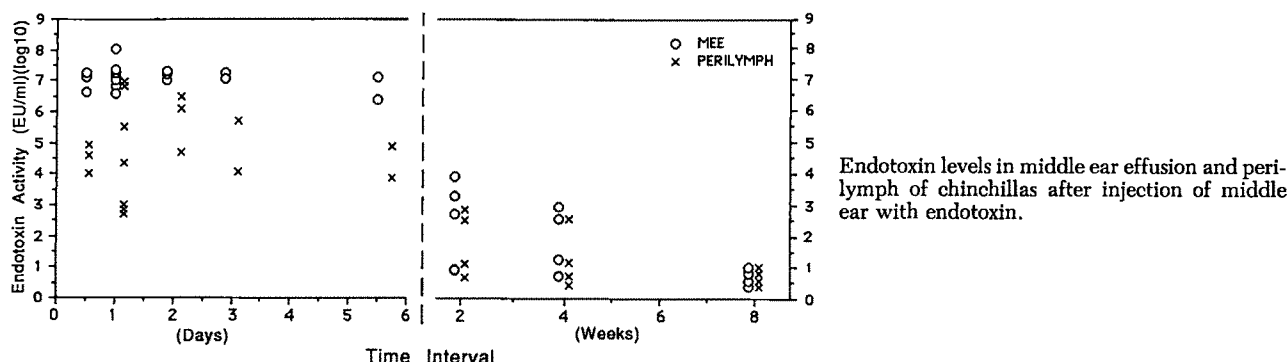
Endotoxin persisted in MEEs and perilymph for up to 3 weeks postinjection, but the concentration was approximately half that observed during the first week of the experimental period (see Figure). One animal had trace amounts of endotoxin in its perilymph 8 weeks postinjection.

HISTOLOGIC FINDINGS

The most common pathologic changes observed in the cochlea during the first week after instillation of endotoxin into the middle ear were inflammatory cell infiltration in the endolymphatic sac, cell infiltration and bleeding in the perilymphatic space (scalae tympani, scalae vestibuli, and spiral ligament), stria swelling, sensory cell degeneration, and endolymphatic hydrops. Although the inflammatory response in the inner ear had resolved 8 weeks after endotoxin instillation, residual endolymphatic hydrops and sensory cell degeneration were seen in the cochleas of many animals. Endo-

From the Otolological Research Laboratories, Department of Otolaryngology, College of Medicine, The Ohio State University, Columbus, Ohio. Supported in part by National Institutes of Health/National Institute of Neurological and Communicative Disorders and Stroke grant NS 08854, the Deafness Research Foundation, and the Japanese Government (fellowship support for H.K.). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The Ohio State University.

REPRINTS — David J. Lim, MD, 456 W 10th Ave, Room 4331 UHC, Columbus, OH 43210.



lymphatic hydrops was observed in almost 50 % of the animals, and two animals showed marked endolymphatic hydrops.

These findings may have significant clinical implications. If endotoxin in the human middle ear can penetrate the round window membrane, penetration would be expected to occur in the acute stage of infection. When endotoxin penetrates the inner ear, it may cause inner ear damage, including hydrops, without leaving evidence of prior inflammation after 4 weeks. Although the human round window membrane is four times as thick (about 56 to 65 μm)⁹ as that of the chinchilla membrane and may not be as permeable to endotoxin, it is tempting to speculate that the high incidence of sensorineural hearing loss and hydrops reported¹⁰ may be the result of a bacterial toxin, such as endotoxin, penetrating the round window membrane. This speculation is credible if one considers the high inci-

dence of appreciable amounts of endotoxin detected in the chronic MEEs of children suffering from chronic otitis media with effusion (secretory otitis media).⁴

In conclusion, we demonstrated that endotoxin in the middle ear cavity can penetrate the round window membrane and induce pathologic changes in the chinchilla inner ear — a response that subsided 2 weeks after endotoxin was instilled. The results support the possibility that endotoxin released in the tympanic cavity from otitis media gram-negative bacterial pathogens, such as *H influenzae* and *Moraxella catarrhalis*, contributes not only to prolonged middle ear inflammation but also to short-term inner ear inflammation resulting in residual endolymphatic hydrops and sensory cell damage. Recent findings indicate that the human round window membrane is permeable to macromolecules.¹¹ It is plausible that the same pathologic changes observed in this study can occur in humans.

REFERENCES

1. Brummett RE, Harris RF, Lindgren JA. Detection of ototoxicity from drugs applied topically to the middle ear space. *Laryngoscope* 1976;86:1177-87.
2. Smith BM, Myers MG. The penetration of gentamicin and neomycin into perilymph across the round window membrane. *Otolaryngol Head Neck Surg* 1979;87:888-91.
3. Harada T, Iwamori M, Nagai Y, Nomura Y. Ototoxicity of neomycin and its penetration through the round window membrane into the perilymph. *Ann Otol Rhinol Laryngol* 1986;95:404-8.
4. DeMaria TF, Prior RB, Briggs BR, Lim DJ, Birek HG. Endotoxin in middle ear effusion from patients with chronic otitis media with effusion. *J Clin Microbiol* 1984;20:15-7.
5. Iino Y, Kaneko Y, Takasaka T. Endotoxin in middle ear effusions tested with limulus assay. *Acta Otolaryngol (Stockh)* 1985;100:42-50.
6. Bernstein JM, Praino MD, Neter E. Detection of endotoxin in ear specimens from patients with chronic otitis media by means of limulus amoebocyte test. *Can J Microbiol* 1980;26:645-8.
7. DeMaria TF, Yamaguchi Y, Lim DJ. Quantitative cytological and histological changes in the middle ear after the injection of nontypable *Hemophilus influenzae* endotoxin. *Am J Otolaryngol* 1989;10:261-6.
8. Kawauchi H, DeMaria TF, Lim DJ. Endotoxin permeability through the round window. *Acta Otolaryngol [Suppl] (Stockh)* 1989(suppl 457):100-15.
9. Nomura Y. Otological significance of the round window. In: Pfaltz CR, ed. *Advances in otorhinolaryngology*. Basel, Switzerland: S Karger, 1984:1-162.
10. Paparella MM, Oda M, Hiraide F, Brady D. Pathology of sensorineural hearing loss in otitis media. *Ann Otol Rhinol Laryngol* 1972;81:632-47.
11. Goycoolea MV, Muchow D, Martinez GC, et al. Permeability of the human round-window membrane to cationic ferritin. *Arch Otolaryngol Head Neck Surg* 1988;114:1247-51.

OUTER HAIR CELLS AS POTENTIAL TARGETS OF INFLAMMATORY MEDIATORS

MAY HUANG, MD

DIDIER DULON, PHD

JOCHEN SCHACHT, PHD

ANN ARBOR, MICHIGAN

Inner ear sequelae with temporary or permanent sensorineural hearing loss can result from inflammatory processes in the middle ear. Loss of outer hair cells in the base of the cochlea has been noted in otitis media, but it is not known how this damage occurs. Evidence supports the permeability of the round window membrane to substances mediating inflammation in the middle ear, and the presence of white blood cells has been reported in the perilymph. In the present study, the potential cytotoxic effects of two representative inflammatory mediators, endotoxin and free radicals, have been evaluated by use of short-term culture of isolated outer hair cells from the guinea pig cochlea model. Incubation with endotoxins from two gram-negative pathogens increased the rate of hair cell death fourfold to sixfold. Free radicals (generated by exposure of cells to UV light or by excitation of intracellular fluorescent dyes) produced morphologic damage to hair cells within 60 seconds. These latter effects were delayed by addition of free-radical scavengers. It is concluded that inflammatory mediators are cytotoxic to hair cells and therefore are potentially ototoxic if permeating the round window membrane.

KEY WORDS — endotoxin, free radicals, inner ear, otitis media, round window membrane.

INTRODUCTION

Conductive hearing loss has been recognized as the primary hearing deficit in otitis media. In addition, there have been suggestions that inner ear sequelae with temporary or permanent sensorineural hearing loss can accompany inflammatory processes in the middle ear, and loss of outer hair cells from the basal turn of the cochlea has been reported.¹ This may be related to the diffusion of antibiotics, toxins, or macromolecules from the middle ear into the perilymph through the semipermeable round window membrane.²⁻⁴ Reactive inflammatory cells also have been found in the perilymph near the round window membrane.¹ However, biochemical mechanisms of inner ear damage resulting from otitis media have not been addressed.

A variety of inflammatory mediators are present in the middle ear during acute and chronic otitis media. These include the microorganisms themselves,⁵ their metabolic products or cell wall remnants, and the invading phagocytic inflammatory cells (eg, polymorphonuclear leukocytes and macrophages).^{6,7} Specific metabolic inflammatory mediators include endotoxins,^{7,8} exotoxins,⁹ arachidonic acid metabolites (prostaglandins),¹⁰ histamines,¹¹ and free radicals.¹² The proximity of the cochlea to the inflamed middle ear and the permeability of the round window membrane warrant a thorough evaluation of the ototoxic potential of these agents.

Investigating the mechanisms by which inflammatory mediators damage the inner ear in otitis media necessitates a suitable model for determining ototoxicity. Outer hair cells are apparently very

sensitive to noxious stimuli. Their loss has been demonstrated in conjunction with aminoglycoside antibiotics,¹³ chemotherapeutic agents such as cisplatin,¹⁴ and acoustic trauma.¹⁵ Since outer hair cells are easily isolated from the cochlea and maintained in vitro,¹⁶ their short-term culture represents a useful model for investigating inner ear disorders. With use of isolated hair cells, it has been demonstrated, for example, that aminoglycosides interfere with calcium binding and the phosphoinositide pathway and, thus, possibly the generation of intracellular second messenger signals.¹⁷ Outer hair cells also undergo shape changes when subjected to osmotic stress — a reaction that may be pertinent in Meniere's disease.¹⁸

In this study, the pathophysiologic responses of isolated hair cells to endotoxins and free radicals, two representative inflammatory mediators, were investigated to evaluate their potential ototoxicity.

RESULTS

Cytotoxicity of Endotoxins. Apical hair cells from the guinea pig cochlea are approximately 70 to 90 μm long and 8 to 10 μm in diameter. At the light microscopic level, the viable hair cells in vitro are characterized by a long cylindrical cell shape, smooth regular membrane, apical stereocilia, basally located nucleus, and the absence of cytoplasmic granularity or swelling (Fig 1A¹⁶). In contrast, non-viable hair cells exhibit cytoplasmic granularity, swelling, and displacement of their nuclei (Fig 1B). As a quantitative and objective measurement, viability was determined with the fluorescent DNA

From the Kresge Hearing Research Institute and the Department of Otolaryngology, University of Michigan, Ann Arbor, Michigan. Supported by National Institutes of Health research grant NS 13792 and training grant T32 NS 07293.

REPRINTS — Dr Jochen Schacht, Kresge Hearing Research Institute, Dept of Otolaryngology, University of Michigan, 1301 E Ann St, Ann Arbor, MI 48109-0506.

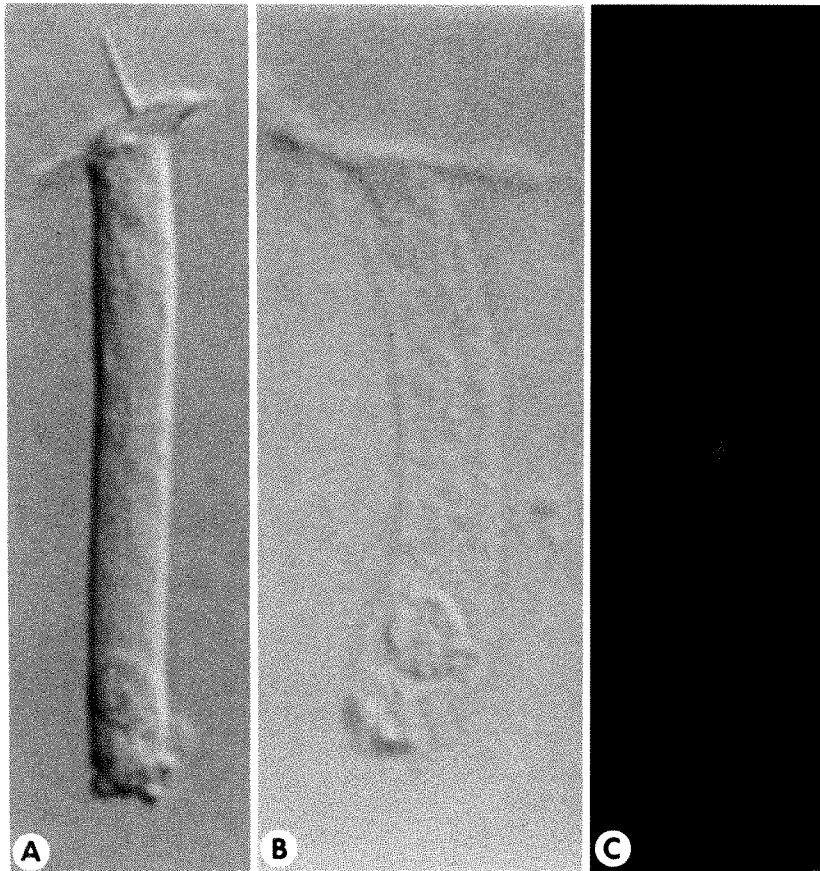


Fig 1. Viable and nonviable isolated outer hair cells. A) Viable outer hair cell at start of incubation (approximately 30 minutes after isolation). Outer hair cells were isolated non-enzymatically from second through fourth cochlear turns of pigmented guinea pigs by microdissection. They were collected and incubated at room temperature in Hank's buffered salt solution without bicarbonate, buffered with 5 mmol/L HEPES to pH 7.40, and adjusted to 300 mOsm (as described by Zajic and Schacht¹⁶). Note elongated shape (70 to 90 μ m length, approximately 10 μ m diameter), presence of stereocilia, basal nucleus, and absence of cytoplasmic granularity or swelling. B) Nonviable outer hair cell after 60-minute incubation with *Escherichia coli* endotoxin at 0.5 μ g/50 μ L Hank's buffered salt solution. Cytoplasmic granularity, swelling, and partial dissolution of plasma membrane are apparent. C) Nonviable hair cell after treatment with 1 μ mol/L propidium iodide. Red fluorescence of nucleus is indicative.

probe propidium iodide. Propidium iodide is excluded by intact cell membranes and only enters nonviable cells, staining their nuclei with a red fluorescence (Fig 1C). After isolation, viable cells constituted 73% to 82% of cell populations (Fig 2). The presence of 0.5 μ g endotoxin in the incubation medium produced no immediate effects. However, cultures exposed to endotoxin for 60 minutes showed a marked increase in the percentage of nonviable cells (80% and 76% nonviable cells for endotoxin from *Escherichia coli* and *Serratia marcescens*, respectively) in comparison to controls (37% nonviable). Endotoxins produced partial dissolution of the plasma membrane, cytoplasmic granularity, and shortening or swelling (Fig 3A). With fluorescently tagged endotoxin from *E coli* or *S marcescens*, binding to isolated hair cells was consistently observed (Fig 3B). The labeling was diffuse throughout the cytoplasm, with higher initial concentrations at the apical end and around the nucleus.

Cytotoxicity of Free Radicals. Free radicals were generated in the cells and in the medium exposed to UV light or by excitation of fluorescent dyes. Isolated outer hair cells showed shortening, cytoplasmic swelling, and granularity within 60 seconds after exposure to near-UV light of 340 to 380 nm (Fig 4). Cells loaded with the dyes 2',7'-bis-(2 carboxyethyl)-5-(and -6)carboxyfluorescein, acetoxy-methyl ester (BCECF-AM) or fura 2-am exhibited

normal morphologic characteristics, but lost their viability after the dyes were excited by exposure to high-intensity blue light or UV light, respectively. The addition of either free-radical scavenger, *p*-phenylenediamine or *N*-propyl gallate (at 1 mmol/L), to the medium 10 minutes prior to expo-

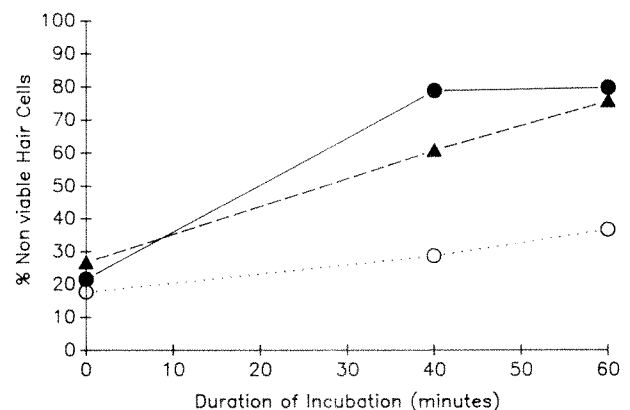


Fig 2. Time course of cytotoxic effects of endotoxins. Outer hair cells were incubated in 50 μ L with fluorescein-labeled endotoxins from *Escherichia coli* serotype 0127:B8 or *Serratia marcescens* at 0.5 μ g/50 μ L Hank's buffered salt solution in humidified petri dishes at room temperature. At end of incubation period, propidium iodide at final concentration of 1 μ mol/L was used to label nonviable cells. Points represent means of triplicate determinations, with 20 to 80 cells counted per droplet; standard deviations did not exceed 12%. Open circles — controls, filled circles — incubation with endotoxin from *E coli*, triangles — incubation with endotoxin from *S marcescens*.

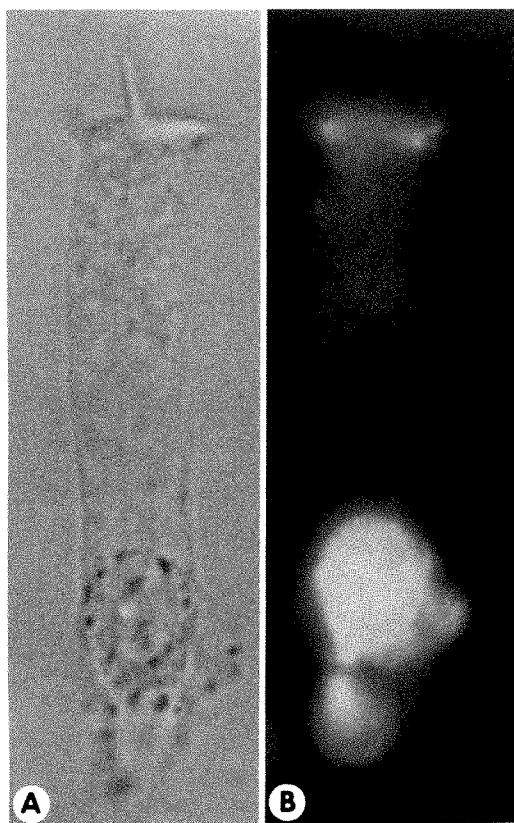


Fig 3. Outer hair cell fluorescently labeled by endotoxin from *Serratia marcescens*. Outer hair cells were incubated for 60 to 120 minutes in humidified petri dishes in 50- μ L droplets containing fluoroisothiocyanate endotoxins (Sigma, St Louis, Mo) from *Escherichia coli* serotype 0127:B8 or *Serratia marcescens* at 0.5 μ g/50 μ L in buffered Hank's buffered salt solution at room temperature. A) Outer hair cell damaged after incubation with *S marcescens* endotoxin for 60 minutes. Note granularity of cytoplasm, swelling, and partial dissolution of membrane. B) Outer hair cell labeled after incubation for 60 minutes with fluorescein isothiocyanate endotoxin from *S marcescens*. Pattern of fluorescent labeling of outer hair cells was similar for both endotoxins.

sure delayed the cellular damage both by UV light (for 3 minutes) and by excited dyes (for 5 minutes).

DISCUSSION

Endotoxin and free radicals are profoundly cytotoxic to hair cells in vitro. The cytotoxic effect of endotoxins is independent of the organism from which they are derived, and the concentrations used here are considerably less than those needed to produce otitis media experimentally.⁸ In the clinical setting, endotoxins arise from gram-negative pathogens of otitis media such as *Hemophilus influenzae* and *Moraxella catarrhalis*. The basic components of endotoxins, lipopolysaccharide cell wall constituents, are similar for most gram-negative bacteria: lipid A (toxic moiety), core oligosaccharide, and O-specific polysaccharide side chains.¹⁹ Endotoxins introduced experimentally into the middle ear can be detected in the perilymph and have been associated with a mild hearing loss in the 6- to 30-kHz range.¹ Dam-

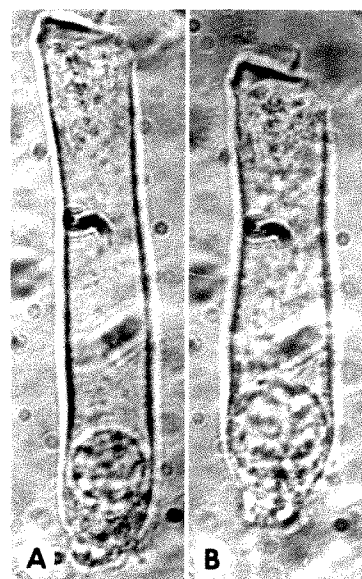


Fig 4. Outer hair cell damaged by exposure to free radicals. A) Isolated outer hair cell prior to exposure to UV light. B) Outer hair cell after 60-second exposure to near-UV light (340 to 380 nm). Note cellular shortening and granular cytoplasm. Similar results were obtained when outer hair cells were incubated in either 1 μ mol/L carboxy-fluorescein tetramethyl ester (BCECF-AM) or fura 2-am for 15 minutes at room temperature and then exposed to high-intensity blue light or UV light, respectively.

age to outer hair cells may well result from an action on their plasma membrane as observed in this study.

Endotoxin or incomplete cell envelope remnants are released upon lysis of the microorganism and may induce the migration of polymorphonuclear leukocytes to the inner ear during otitis media. These phagocytic cells use molecular oxygen in their bactericidal actions to form superoxide radicals and other reactive oxygen species.¹² These reactive oxygen species are secreted both into the phagocytic vacuoles and into the extracellular environment. Trace transition metal ions may serve as additional mediators for the formation of hydroxyl radicals from released hydrogen peroxide.

Experimentally, free radicals can be produced by exposure to UV light and by chemical or enzymatic methods. Both UV light and the excitation of the fluorescent dyes BCECF-AM and fura 2-am (commonly used in determining intracellular pH and calcium, respectively) appear to cause cytotoxicity by forming reactive oxygen species. This hypothesis is suggested by the delay of morphologic damage in the presence of either radical scavenger, *p*-phenylenediamine or *N*-propyl gallate. In tissues, the enzymes superoxide dismutase, catalase, and glutathione peroxidase inactivate free radicals and thus protect intracellular targets such as lipids, proteins, and DNA from damage. The organ of Corti and stria vascularis have been reported to contain all three enzymes.²⁰ In the pathologic case, it might be

speculated that the free radicals produced extracellularly by polymorphonuclear leukocytes — in a different location and at higher concentrations than in normal metabolism — exceed the capacity of the inner ear enzymes to remove them. Although conclusive evidence is lacking, such a mechanism has been postulated for the ototoxicity induced by aminoglycosides²¹ and cisplatin.²² It has been suggested that administration of free-radical scavengers in vivo may offer protection against certain ototoxic agents. Therefore, free radicals may be part of a

common mechanism of damage to inner ear cells.

The results obtained here substantiate the usefulness of isolated outer hair cells as models for the investigation of ototoxicity. They show that endotoxins and free radicals, both products of chronic otitis media with effusion, are directly cytotoxic to cochlear sensory cells. Although preliminary, the results suggest that such a mechanism may play a role in mediating temporary or permanent sensorineural hearing loss in otitis media.

REFERENCES

1. Paparella MM, Oda M, Hiraide F, Brady D. Pathology of sensorineural hearing loss in otitis media. *Ann Otol Rhinol Laryngol* 1972;81:632-47.
2. Goycoolea MV, Muchow D, Schachern P. Experimental studies on round window membrane structure, function and permeability. *Laryngoscope* 1988;98(suppl 44).
3. Lundman LA, Holmquist L, Bagger-Sjöbäck D. Round window membrane permeability: an in vitro model. *Acta Otolaryngol (Stockh)* 1987;103:1-9.
4. Goycoolea MV, Muchow D, Martinez GC, et al. Permeability of the human round-window membrane to cationic ferritin. *Arch Otolaryngol Head Neck Surg* 1988;114:1247-51.
5. Reilly JS, Doyle WJ, Cantekin EI, Supance JS, Rohn DD. Pathogenic potential of microorganisms to cause acute otitis media with effusion in chinchillas. *Ann Otol Rhinol Laryngol* 1983;92(suppl 107):28.
6. Giebink GS, Ripley-Petzoldt ML, Juhn SK, Aeppli D, Tomasz A, Tuomanen E. Contribution of pneumococcal cell wall to experimental otitis media pathogenesis. *Ann Otol Rhinol Laryngol* 1988;97(suppl 132):28-30.
7. DeMaria TF, Priot RB, Briggs BR, Lim DJ, Birck HG. Endotoxin in middle ear effusions from patients with chronic otitis media with effusion. *J Clin Microbiol* 1984;20:15-7.
8. Nonomura N, Nakano Y, Satoh Y, Fujioka O, Nijima H, Fujita M. Otitis media with effusion following inoculation of *Haemophilus influenza* type b endotoxin. *Arch Otorhinolaryngol* 1986;243:31-5.
9. Goycoolea MV, Paparella MM, Goldberg B, Schlievert PM, Carpenter A-M. Permeability of the middle ear to staphylococcal pyrogenic exotoxin in otitis media. *Int J Pediatr Otorhinolaryngol* 1980;1:301-8.
10. Jung TTK. Arachidonic acid metabolites in otitis media pathogenesis. *Ann Otol Rhinol Laryngol* 1988;97(suppl 132):14-8.
11. Skoner DP, Stillwagon PK, Casselbrant ML, Tanner EP, Doyle WJ, Fireman P. Inflammatory mediators in chronic otitis media with effusion. *Arch Otolaryngol Head Neck Surg* 1988;114:1131-3.
12. Lunec J, Griffiths HR, Blaker DR. Oxygen radicals in inflammation. *ISI Atlas Sci: Pharmacology* 1987;1:45-8.
13. Forge A. Outer hair cell loss and supporting cell expansion following chronic gentamicin treatment. *Hear Res* 1985;19:171-82.
14. Horn JW, Sheridan CE, Dolan DF, Hawkins JE Jr, Aran J-M, Altschuler RA. Ultrastructural effects of cis-platinum on guinea pig outer hair cells. *Abstr 11th Midwinter Meeting*, Jan 31-Feb, 1988;abstract 173:143-4.
15. Slepecky N. Overview of mechanical damage to the inner ear: noise as a tool to probe cochlear function. In: Flock A, Wersäll J, eds. *Cellular mechanisms in hearing*. Amsterdam, the Netherlands: Elsevier Science Publishers, 1986:307-22.
16. Zajic G, Schacht J. Comparison of isolated outer hair cells from five mammalian species. *Hear Res* 1987;26:249-56.
17. Williams SE, Zenner HP, Schacht J. Three molecular steps of aminoglycoside ototoxicity demonstrated in outer hair cells. *Hear Res* 1987;30:11-8.
18. Dulon D, Aran J-M, Schacht J. Osmotically induced motility of outer hair cells: implications for Ménière's disease. *Arch Otorhinolaryngol* 1987;244:104-7.
19. DeMaria TF. Endotoxin and otitis media. *Ann Otol Rhinol Laryngol* 1988;97(suppl 132):31-3.
20. Pierson MG, Gray BH. Superoxide dismutase activity in the cochlea. *Hear Res* 1982;6:141-51.
21. Pierson MG, Moller AR. Prophylaxis of kanamycin-induced ototoxicity by a radioprotectant. *Hear Res* 1981;4:79-87.
22. Otto WC, Brown RD, Gray-White L, et al. Effects of cisplatin and thiosulfate upon auditory brainstem responses of guinea pigs. *Hear Res* 1988;35:79-86.

CLINICAL PERSPECTIVES ON OTOTOXIC DRUGS

GREGORY J. MATZ, MD

CHICAGO, ILLINOIS

Ototoxic drugs such as salicylates, the aminoglycoside antibiotics, loop diuretics, cisplatin, erythromycin, and vancomycin are widely used in clinical practice. The most commonly used are aspirin and the aminoglycoside antibiotics. This chapter briefly discusses the pharmacology of the commonly prescribed ototoxic drugs and the doses that may result in ototoxicity. An outline for the monitoring of ototoxic drugs is presented. The role of topical ear drops as a possible cause of ototoxicity is reviewed.

KEY WORDS — aminoglycosides, ear drops, ototoxic drugs, salicylates.

In the United States, the frequency of ototoxic manifestations of drugs used in clinical practice has decreased in the typical otologic practice. However, a recent newspaper article¹ stated that at least a quarter of a million Chinese children developed significant hearing loss related to toxicity of streptomycin, gentamicin, and kanamycin. These drugs were frequently prescribed to treat pneumonia, diarrhea, or tuberculosis in the People's Republic of China, and Beijing health experts believed these drugs were overprescribed. They stated that only 2% of childhood deafness in the 1950s was caused by drug ototoxicity, but that drugs are now responsible for 35% of the 670,000 cases of deafness in preschool children.

Physicians need to be familiar with auditory and vestibular drug toxicity for two reasons: 1) to recognize that a specific hearing loss or vestibular symptom complex may be a direct consequence of an ototoxic drug and 2) to be familiar with drug ototoxicity and eliminate this as a possible source of hearing loss in their practices.

AMINOGLYCOSIDES

Aminoglycoside antibiotics are poorly absorbed from the digestive tract; only 3% of these drugs are absorbed directly into the bloodstream. Tissue concentrations of aminoglycosides are usually one third of serum concentrations, and these drugs cross the blood-brain barrier negligibly except in neonates. Aminoglycosides are not metabolized, and they are excreted almost exclusively by glomerular filtration; therefore, concentrations in the urine may reach higher levels than those in serum. Aminoglycoside antibiotics can concentrate in perilymph, especially in individuals with impaired renal function, such as during longer treatment schedules in patients with renal failure. The higher aminoglycoside concentrations in perilymph may cause ototoxicity, an effect that might be minimized if the interval between parenteral doses is long enough for clearance from perilymph. The exact route by

which aminoglycosides reach the hair cells of the inner ear from the bloodstream is not known, although it is known they are transported to the cell by an energy-dependent process in which drug is bound to phosphatidylinositol biphosphate, a physiologically important phospholipid.² Once inside the cell, the aminoglycosides may interfere with further intracellular reactions. Schacht² proposed a six-step process. First, the aminoglycoside reacts with a negatively charged ion at the outer plasma membrane. The aminoglycosides usually replace calcium or magnesium in this process. The drugs are then transported into the cell by the energy-dependent process and are bound to the phosphatidylinositol biphosphate complex, a process that inhibits other reactions regulated by phosphoinositides, such as synthesis of prostaglandins.

There is a great deal of evidence that the ototoxicity of aminoglycoside antibiotics is enhanced by concomitant therapy with a loop diuretic, such as ethacrynic acid or furosemide.³ A number of animal studies have shown striking ototoxic synergy between loop diuretics and aminoglycosides.

There is extensive literature in both retrospective and prospective studies comparing the ototoxicity and nephrotoxicity of aminoglycoside antibiotics. Studies by Fee,⁴ Smith et al,^{5,6} and Learner et al⁷ indicate that the ototoxicity rates of newer aminoglycosides, such as gentamicin, tobramycin, netilmicin, and amikacin, are similar to but lower than the rates of the "older" aminoglycosides streptomycin, kanamycin, and neomycin.

Kahlmeter and Dahlager⁸ reviewed the clinical studies published between 1975 and 1982 on over 10,000 patients. The average incidence of nephrotoxicity was 14% for gentamicin, 12.9% for tobramycin, 8.7% for netilmicin, and 9.4% for amikacin. The average incidence of cochlear toxicity in these studies was 13.9% for amikacin, 8.3% for gentamicin, 6.1% for tobramycin, and 2.4% for netilmicin. Some of these studies suffered from ab-

From the Department of Otolaryngology, Loyola University, Chicago, Illinois. Supported in part by a grant from the Schering Corporation, Rahway, New Jersey.

REPRINTS — Gregory J. Matz, MD, Dept of Otolaryngology, Loyola University, 2160 S First Ave, Maywood, IL 60153.

sence of investigator blinding or a low proportion of subjects available for auditory tests, and, in many instances, vestibular function tests, thus presenting evidence for lower toxicity than actually existed.

Controversy exists as to whether the aminoglycosides are a significant cause of early-onset hearing impairment in infants. Extensive reviews and studies by Finitzo-Hieber et al⁹ indicate that aminoglycoside antibiotics rarely cause ototoxicity in children. On the basis of a number of prospective, controlled longitudinal studies that attempted to assess aminoglycoside-associated ototoxicity in neonates by use of netilmicin, amikacin, and gentamicin, the risk of developing significant hearing impairment during a 3- to 7-day course of aminoglycoside therapy is small. Kumor et al¹⁰ reported similar findings with high-dose amikacin in children.

Numerous studies over the years have attempted to determine whether monitoring high-frequency auditory function would predict aminoglycoside ototoxicity. Rappaport et al¹¹ presented data on a prospective study of long-term oral neomycin in adults whose high-frequency sensitivity was serially monitored. In this excellent study, only 2 of 30 patients demonstrated ototoxic change.

Numerous prospective studies have examined risk factors for ototoxicity such as duration of therapy, peak and trough serum levels, age, and concomitant use of other drugs. Compromised renal function still plays an important role in causing clinical ototoxicity. There are many clinical reports documenting the association of poor renal function with ototoxic antibiotics and eighth nerve disease, and dose reduction is still suggested in prescribing aminoglycosides in patients with renal disease.

It is unclear if use of topical ear drops is a frequent cause of clinical ototoxicity. Neomycin ear drops, for example, do not seem to be associated with a high risk of ototoxicity in humans. However, numerous studies at the University of Minnesota¹² document very well the ototoxicity of not only neomycin but also chloramphenicol and other medications, as well as vehicles used in these medications in animals. Solutions introduced into the chronically infected human middle ear are probably not absorbed into the cochlea to any significant degree. Whether this is due to the oblique orientation of the human round window membrane or to poor penetration through the chronically infected middle ear tissue is not certain. It is clear, however, that the clinician rarely sees ototoxicity related to topical use of ear drops (see bottom p 41). The concept should not be ignored, since the possibility of topical antibiotic ototoxicity is real. Therefore, ear drops should be used with caution in patients with tympanic membrane perforations, patients should not be allowed to obtain unlimited ear drop refills, and these drugs should not be used without medical sur-

veillance.

LOOP DIURETICS

Loop diuretics such as furosemide, ethacrynic acid, and bumetanide are commonly used in medical practice. Furosemide, for example, is commonly used to treat hypertension, as well as cardiac, renal, and hepatic failure. The exact incidence of hearing loss related to loop diuretics is not known. In a large series, rates of ototoxicity were 0.7% for ethacrynic acid, 1.1% for bumetanide, and 6.4% for furosemide.¹³ Furosemide toxicity can be reduced by adjusting the infusion rate to less than 15 mg/min. Ototoxic synergy between loop diuretics and aminoglycosides has been demonstrated in many studies.

SALICYLATES

It has been known for years that salicylate treatment can result in transient hearing loss. Permanent loss, however, has not been clearly documented, and an excellent electron microscopy study by Deer and Hunter-Divar¹⁴ showed no cell destruction in laboratory animals receiving high doses of salicylates. Salicylates in perilymph can cause a reduction in transaminases, decreased cochlear adenosine triphosphate levels, and decreased cochlear blood flow.¹⁵ I have personally seen no clinical cases of permanent hearing loss due to high doses of salicylates. Usually, when the salicylate level exceeds 20 mg/dL, patients develop transient hearing loss and significant tinnitus. In general, the only patients who develop salicylate symptoms are those receiving 40 to 60 grains a day for treatment of rheumatoid arthritis. The various temporal bone studies reported over the years have described only postmortem changes and not changes that can be attributed to salicylates.

CISPLATIN

Cisplatin is commonly used for adjuvant and induction chemotherapy for squamous cell carcinoma of the head and neck and for treating other malignancies. Ototoxicity is related to decrease of the adenylate cyclase in the inner ear and resulting outer hair cell loss, especially at the cochlear base. Whenever dosage exceeds 3 to 4 mg/kg of body weight, toxicity can occur. Both vestibular and cochlear toxicity has been described with cisplatin, and permanent hearing loss can result from use of this cancer chemotherapeutic agent. Bilateral loss is most common with initial losses in the high-frequency range, resembling aminoglycoside toxicity. Rates of toxicity range as high as 20%. Otic disorders have been described by Strauss et al¹⁶ with permanent changes in the outer hair cells and other areas of the organ of Corti.

ERYTHROMYCIN

Erythromycin was not considered an ototoxic drug until it was used for treating pneumonias caused by *Legionella pneumophila* and related

pathogens. Most reported cases have involved bilateral sensorineural hearing loss, especially in patients with hepatic and renal failure¹⁷ when a dose exceeding 2 g of erythromycin daily was used. The typical symptoms of tinnitus, vertigo, and hearing loss, especially in elderly patients, were noted in patients receiving large doses of intravenous erythromycin. Ototoxic blood levels were noted to be in the range of 63 mg/L or more, and in some instances, auditory changes were observed after erythromycin was discontinued.

VANCOMYCIN

Vancomycin is both nephrotoxic and ototoxic. Hearing loss in humans has been reported,¹⁸ especially when blood levels exceed 45 mg/L. Tinnitus has been associated with peak serum levels of 40 to 50 mg/L. Risk of vancomycin ototoxicity appears to be greater in persons older than 65 years of age, especially in patients with reduced renal function who are receiving other potentially ototoxic drugs. Premature infants are especially susceptible, since

they have longer vancomycin half-lives and larger volumes of distribution than full-term infants.

MONITORING OF OTOTOXIC DRUGS

In monitoring ototoxic drugs, several special situations or high-risk groups should be singled out for periodic auditory and vestibular testing.¹⁹

1. Patients with impaired renal function either before or during therapy.
2. Patients with elevated peak and trough serum levels of ototoxic drugs.
3. Patients with preexisting sensorineural hearing loss, especially from ototoxic drugs.
4. Patients receiving more than one ototoxic drug or having a history of ototoxic drug use.
5. Patients for whom a treatment course in excess of 14 days is planned.
6. Patients in whom symptoms suggestive of cochlear or vestibular toxicity become evident.
7. Patients receiving any combination of aminoglycosides and loop diuretic drugs.

REFERENCES

1. Chicago Tribune, Nov 24, 1988, Sec 1, 41.
2. Schacht J. Molecular mechanisms of drug-induced hearing loss. *Hear Res* 1986;48:297-304.
3. Brummett RE, Traynor J, Brown R, Himes DL. Cochlear damage resulting from kanamycin and furosemide. *Acta Otolaryngol* (Stockh) 1975;80:86-92.
4. Fee WE Jr. Aminoglycoside ototoxicity in the human. *Laryngoscope* 1980;90(suppl 24).
5. Smith CR, Lipsky JJ, Laskim DB, et al. Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. *N Engl J Med* 1980;302:1106-9.
6. Smith CR, Baughman KL, Edwards CQ, Rogers JF, Lietman PS. Controlled comparison of amikacin and gentamicin. *N Engl J Med* 1977;96:349-53.
7. Learner SA, Seligsohn R, Rudd R, Matz GJ. Comparative clinical studies of ototoxicity and nephrotoxicity of amikacin and gentamicin. *Am J Med* 1977;62:919-23.
8. Kahlmeter O, Dahlager JI. Aminoglycoside toxicity — a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984;13(suppl A):9-22.
9. Finitzo-Hieber T, McCracken GH Jr, Brown KC. Prospective controlled evaluation of auditory functions in neonates given netilmicin or amikacin. *J Pediatr* 1985;106:129-36.
10. Kumor KM, McDonald JM, Lietman PS. Effect of "high-dose" amikacin in children. *Dev Pharmacol Ther* 1984;7:368-76.
11. Rappaport BZ, Fausti SA, Schechter MA, Frey RH. A prospective study of high-frequency auditory function in patients receiving oral neomycin. *Scand Audiol* 1986;15:67-71.
12. Morizono T. Ototoxic agents: ototoxicity in animal studies. *Ann Otol Rhinol Laryngol* 1988;97(suppl 131):28-30.
13. Boston Collaborative Drug Surveillance Program. Drug-induced deafness. *JAMA* 1973;224:515-9.
14. Deer BC, Hunter-Divar I. Salicylate ototoxicity in the chinchilla: a behavioral and electron microscope study. *J Otolaryngol* 1982;11:260-6.
15. Hawkins JE Jr. Ototoxic mechanism — a working hypothesis. *Audiology* 1973;12:383-7.
16. Strauss M, Towfighi J, Lord S, Lipton A, Harvey HA, Brown B. Cisplatin ototoxicity: clinical experience and temporal bone histopathology. *Laryngoscope* 1983;93:1554-9.
17. Kroboth PD, McNiel MA, Kreeger A, Dominguez J, Rault R. Hearing loss and erythromycin pharmacokinetics in a patient receiving hemodialysis. *Arch Intern Med* 1983;143:1263-6.
18. Rybak LP, Boicke SC. Additive toxicity in patients receiving vancomycin and aminoglycosides. *Clin Pharm* 1983;2:508-11.
19. Rybak LP, Matz GJ. Ototoxicity. In: Rubin R, Alberto P, eds. *Otologic medicine and surgery*. New York, NY: Churchill Livingstone, 1988:1623-35.

This is an important observation for otolaryngologists. H. F. Schuknecht made the same comment at a postgraduate exercise in Minneapolis (1964, personal communication), and I agree. In 30 years of practice I have not recognized a single ear damaged in hearing from any antibiotic ear drop, however long term. This total experience has not changed since then. This comment is important not only for patient care but for medicolegal reasons. — B. F. McCabe, MD, Editor, *Annals of Otolaryngology, Rhinology & Laryngology*.

TOXICITY OF OTOTOPICAL DRUGS: ANIMAL MODELING

TETSUO MORIZONO, MD

MINNEAPOLIS, MINNESOTA

It is important to be aware of the potential ototoxicity of any drug, vehicle, or antiseptic that is used in the middle ear. Frequently used ear drops (Cortisporin otic suspension, Coly-Mycin S Otic, and V5oL otic solution) were studied for their ototoxicity. Compound action potentials were measured before and at 1, 2, and 24 hours following drug application on the round window membranes of chinchillas. Each drug was applied for 10 minutes and then was removed by rinsing. The sound pressure in decibels sound pressure level that produced a compound action potential amplitude of 10 μ V was defined as the threshold. The change in threshold was interpreted as hearing loss. On the basis of the short-term results at 24 hours following drug application, the ototoxicity of Coly-Mycin was calculated to be twice that of Cortisporin, and the ototoxicity of V5oL four times that of Cortisporin.

KEY WORDS — animal models, dose-response curve, ototoxicity.

INTRODUCTION

Sensorineural hearing loss (SNHL) has been described in humans with various forms of otitis media,¹⁻⁷ yet the pathogenesis of this condition is difficult to study in humans because of the many uncontrolled variables. Animal models provide an opportunity to control these variables, and we have demonstrated SNHL in experimental purulent otitis media due to *Streptococcus pneumoniae*.⁸ It is not known, however, whether SNHL occurs during the natural course of otitis media or is caused by topical otic antimicrobial preparations.

Topically applied drugs are commonly used intraoperatively and postoperatively in the ear both for acute and chronic middle ear infections. Many topically applied drugs, vehicles, and antiseptics have been studied for their ototoxicity, and these studies are reviewed elsewhere.⁹ Many drugs that have been used in the past have been found to be ototoxic. When topically applied drugs are used for otitis media with tympanic membrane perforation, there is a potential for the drug to communicate with the inner ear via the round window membrane (RWM). This is also the case when these drugs are used in middle ear surgery. Therefore, it is important to be aware of any potential for ototoxicity of any drug, vehicle, or antiseptic that is used in the middle ear.

MATERIALS AND METHODS

Chinchilla models were developed to learn whether, how, and under what conditions SNHL develops in controlled conditions following ototopical drug application. The method of constructing the audiogram was based on measurements of the action potential and is described elsewhere.⁸ To study the presence and mechanism of SNHL, our laboratory has developed techniques to measure endocochlear DC potential, cochlear microphonics, electrocochleography using compound action potential (CAP), and averaged auditory evoked brain stem potentials. Recently our laboratory established normal data for various ions and partial pressure of oxygen in inner ear fluids using microelectrodes. Micropressure of the inner ear fluids and its dynamic changes also are being measured under various experimental conditions. In the present study, CAP was measured before and after the drug application on the RWM. Fifty microliters of the drug diluted with Ringer's solution was applied on the RWM. Ten minutes after the drug was applied, the area was rinsed twice with 200 μ L of Ringer's solution and dried with a wick made of tissue paper. In the same animal, measurements were repeated at 1, 2, and 24 hours. The results shown in the Tables represent the sound pressure level (SPL) required to produce a 10- μ V threshold of the CAP.

TABLE 1. HEARING LOSS FOLLOWING APPLICATION OF FULL-STRENGTH CORTISPORIN SUSPENSION

Hours After Drug Application	No. of Ears Studied	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	12 kHz
1	17	7.9 $\pm$ 3.3	12.3 $\pm$ 6.9	7.6 $\pm$ 10.6	21.0 $\pm$ 12.2	22.0 $\pm$ 9.3	32.8 $\pm$ 9.4
2	17	3.6 $\pm$ 8.2	15.2 $\pm$ 6.1	16.8 $\pm$ 13.0	32.7 $\pm$ 17.5	28.6 $\pm$ 17.6	35.6 $\pm$ 17.0
24	17	26.2 $\pm$ 11.7	21.8 $\pm$ 16.6	25.7 $\pm$ 18.4	24.4 $\pm$ 18.9	24.6 $\pm$ 21.7	29.0 $\pm$ 20.5

Data (mean $\pm$ SD) represent hearing loss in decibels sound pressure level.

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REPRINTS — Otitis Media Research Center, University of Minnesota, Box 396 UMHC, 420 Delaware St SE, Minneapolis, MN 55455.

TABLE 2. HEARING LOSS FOLLOWING APPLICATION OF FULL-STRENGTH COLY-MYCIN

Hours After Drug Application	No. of Ears Studied	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	12 kHz	16 kHz
1	6	6.2 ± 4.5	8.0 ± 8.3	8.7 ± 3.4	10.9 ± 8.3	13.1 ± 11.8	36.2 ± 20.2	41.6 ± 8.0
2	6	15.9 ± 7.6	19.9 ± 18.2	31.4 ± 16.7	41.5 ± 21.0	44.9 ± 23.8	48.4 ± 19.0	54.7 ± 10.3
24	4	42.8 ± 25.3	48.8 ± 15.7	47.7 ± 15.3	57.9 ± 10.9	61.2 ± 7.9	56.1 ± 15.2	54.2 ± 14.1

Data (mean ± SD) represent hearing loss in decibels sound pressure level.

RESULTS

Ototoxicity of Cortisporin Suspension. Ototoxicity of full-strength Cortisporin suspension was studied in 17 chinchilla ears at 1, 2, and 24 hours after applying the suspension to the RWM (Table 1). The loss for high frequencies was almost complete at 2 hours and was not progressive when measured at 24 hours. This pattern of progress was different from that observed with other drugs. For instance, Betadine and chlorhexidine (Hibitane) caused progressive SNHL for several weeks.¹⁰ Following application of Cortisporin suspension, which contains steroids, inflammatory changes in the middle ear were not pronounced at 24 hours. Reduced inflammation in the middle ear appears to be favorable to the inner ear.

Ototoxicity of Coly-Mycin Ear Drops. Ototoxicity testing of this drug is still in progress, and pilot data are shown in Tables 2 and 3. Coly-Mycin produced a dose-related CAP reduction that progressed with time, initially affecting the higher frequencies but ultimately resulting in a flat hearing loss at 24 hours.

Ototoxicity of VdSoL. At full strength all three animals tested exhibited a complete loss of CAP at 1 hour, 2 hours, and 24 hours. At half strength two of three animals showed completely diminished CAPs at 1 hour, one animal showed a high-frequency loss, and all three animals showed complete losses of CAP at 24 hours. Ototoxicity of VdSoL at one-quarter strength is illustrated in Table 4. Even at one-eighth strength, the CAP threshold was elevated at 24 hours (Table 5).

DISCUSSION

Full-strength Cortisporin caused a hearing loss of about 24 dB at all CAP frequency measurements at 24 hours (Table 1). Coly-Mycin at half strength produced an equivalent hearing loss (Table 2), as did VdSoL at quarter strength. Therefore, Coly-Mycin ototoxicity was twice, and VdSoL ototoxicity four times that produced by Cortisporin suspension.

These results have clinical relevance because otological drugs are commonly used. According to Nelson,¹¹ topical medication was used by 79 % of practicing pediatricians. Of those who prescribed a drug, Cortisporin suspension was the overwhelming favorite of 87 %, and Coly-Mycin was used by 13 %. Some physicians indicated they used two or three drugs. Meyerhoff et al¹² found an attenuation of action potential and hair cell loss when Cortisporin was instilled into the external auditory canal of chinchillas with tympanostomy tubes in place. Wright and Meyerhoff¹³ showed severe loss of hair cells when Cortisporin was instilled directly into the middle ear of chinchillas.

Special considerations must be given in evaluating the ototoxicity and pharmacokinetics of topical otic drugs (see Figure). Drugs applied to the normal middle ear cavity will be eliminated via the eustachian tube. If an excess amount of drug is instilled into the middle ear cavity, the eustachian tube will not be able to eliminate all of the drug in a short period of time. The drug itself may cause tubal dysfunction and may enhance ototoxic potential of the drug. A drug in the middle ear cavity will be absorbed partially by the mucosa and submucosal space, and may cause inflammatory reactions. To date, little is known about the effect of inflammatory changes in the middle ear cavity on the kinetics of otological drugs.

The most salient feature of the pharmacokinetics of otic drops is the presence of the RWM. The RWM is an important portal for the passage of inflammatory mediators, toxins, and drugs from the middle ear to the inner ear.⁷ Its role in the pathogenesis of inner ear complications of otitis media needs to be determined. The RWM may undergo permeability changes resulting from otological drugs or middle ear inflammation, permitting otological drugs and bacterial enzymes to find their way more easily to the perilymph, causing a functional disturbance of hearing. Little is known, however, of the basic permeability of this membrane. It is important to study

TABLE 3. HEARING LOSS FOLLOWING APPLICATION OF HALF-STRENGTH COLY-MYCIN

Hours After Drug Application	No. of Ears Studied	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	12 kHz	16 kHz
1	7	5.8 ± 13.4	0.7 ± 15.5	-6.5 ± 17.0	-1.9 ± 15.7	2.7 ± 17.1	3.3 ± 12.9	17.1 ± 11.2
2	7	3.8 ± 9.2	8.3 ± 20.3	5.0 ± 25.4	2.8 ± 25.9	9.0 ± 24.8	12.8 ± 26.7	16.7 ± 14.1
24	7	19.3 ± 20.6	24.4 ± 25.2	29.7 ± 13.4	15.0 ± 25.0	21.4 ± 24.1	21.2 ± 26.9	20.0 ± 4.3

Data (mean ± SD) represent hearing loss in decibels sound pressure level.

TABLE 4. HEARING LOSS FOLLOWING APPLICATION OF ONE-QUARTER-STRENGTH V6SOL

Hours After Drug Application	No. of Ears Studied	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	12 kHz	16 kHz
1	3	4.4± 6.5	3.2± 7.4	7.7± 11.9	11.2± 12.6	10.1± 12.6	19.1± 15.8	21.4± 11.6
2	3	8.8± 6.5	5.4± 5.3	10.3± 12.1	16.2± 13.7	17.8± 19.5	23.9± 17.9	23.5± 11.5
24	3	27.0± 18.8	19.0± 18.8	20.8± 24.2	27.2± 26.4	26.3± 26.5	26.0± 30.4	22.6± 11.3

Data (mean±SD) represent hearing loss in decibels sound pressure level.

the ability of various substances to cross the RWM to determine if the rate of transfer is altered by the presence of infection or inflammation within the middle ear and to correlate permeability change with cochlear function. These experiments may provide information relative to the genesis of SNHL with otitis media. Similar studies are difficult to perform in humans. The animal studies will provide important information on the role of infection and inflammation in the production of SNHL in otitis media.

The inner ear target tissue of otic drugs will vary depending on the drugs used. Aminoglycosides directly affect the hair cells, probably because of the charge of the drugs. Aminoglycosides do not cause reduction in endocochlear potentials; hence, the stria vascularis is presumably intact. Acetic acid, however, seems to directly affect the stria vascularis, as evidenced by the immediate drop in endocochlear potentials following middle ear application of both 2% acetic acid and V6SOL otic solution.¹⁴

Flow dynamics of the inner ear fluids are not well understood. Although the importance of the endolymphatic sac in regulating immune responses of the inner ear has been advocated, the contribution of the endolymphatic sac in regulating ototoxic effects may be very small, if present at all.

The study of SNHL as a sequela of otitis media is one of the principal efforts of our laboratory. Otitis media is generally known to cause a conductive loss; however, some clinical studies have reported SNHL following otitis media. Therefore, animal studies that allow greater flexibility in controlling different variables are warranted in assessing SNHL as a sequela of otitis media.

In spite of the efforts of several workers, studies of ototoxic drugs have serious problems: 1) it is difficult to distinguish conductive and sensorineural deafness, 2) there is a discrepancy between animal data and human clinical experience, and 3) the de-

gree of ototoxicity of a drug is not specified other than with statements such as "severe" or "slight" damage.

To separate conductive hearing loss and SNHL, a long-term study should be done (when all middle ear inflammation and effusion has subsided). It is our experience that 1 month after Cortisporin instillation into the middle ear cavity, the cavity is usually as clean as the Ringer's solution-washed control side. If severe middle ear inflammation persists, combined deafness will result. Bone conduction testing and action potential tuning curve measurements should yield meaningful data, at least theoretically, but our attempts have not yet yielded satisfactory results.

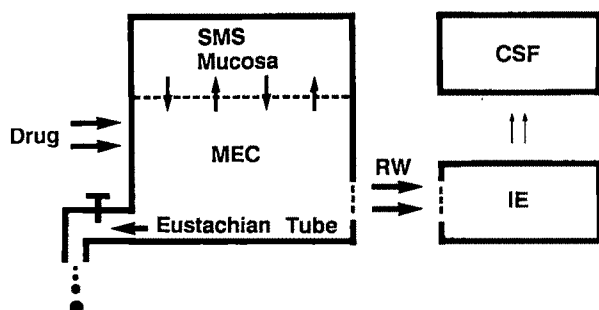
The generally contradictory findings between clinical experience and experimental results may be due to several factors that can be broadly classified as structural and procedural. The structural factors include anatomic differences between humans and experimental animals. The most common laboratory animals used for ototoxicity studies are the guinea pig and chinchilla. Both species have a round window that is vulnerably exposed in the middle ear cavity, unlike the human round window, which is deeply recessed in a narrow niche. Perhaps more important is the thickness difference between the RWMs of the rodent and human. The human membrane is thicker and has a greater collagen density than the rodent membrane. Also, Nomura¹⁵ documented that a pseudomembrane often drapes the human round window. These factors could afford a greater barrier to the passive diffusion of a drug from middle to inner ear.

Higher frequencies are the first to be affected by toxic agents present in the middle ear. Common audiologic practice ignores testing above 8 kHz because of the imprecision of calibration at extra-high frequencies and the greater importance of the "speech frequencies" to humans. Thus, the procedures used in the assessment of hearing loss often ignore just those frequencies most likely to be affected

TABLE 5. HEARING LOSS FOLLOWING APPLICATION OF ONE-EIGHTH-STRENGTH V6SOL

Hours After Drug Application	No. of Ears Studied	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	12 kHz	16 kHz
1	7	1.8±8.7	1.6±3.1	2.7± 3.6	8.3± 7.5	7.5± 9.0	8.0± 9.8	7.6± 8.1
2	7	4.7±4.5	2.3±3.9	3.6± 5.5	11.3± 8.7	6.3± 7.0	12.3±12.2	12.8±10.7
24	7	17.9±6.2	13.3±6.3	14.1±13.2	19.4±12.3	14.3±13.1	17.3±21.1	15.3±14.4

Data (mean±SD) represent hearing loss in decibels sound pressure level.



Pharmacokinetics of topical otic drugs (see text). SMS — submucosal space, MEC — middle ear cavity, RW — round window, IE — inner ear, CSF — cerebrospinal fluid.

by topical agents. The importance of extra-high frequencies in speech recognition should not be ignored.¹⁶

There is a difference in the vulnerability of humans and rodents to topical otic preparations and the potential of toxicity of these preparations in clinical use. The need for experimental examination of topical ototoxicity still exists, but the emphasis should be placed on scaling animal studies to humans and on recommending the least toxic of substances with equivalent clinical efficacy. The degree of ototoxicity can be expressed by employing the modern pharmacologic practice of dose-response curves, as we have reported elsewhere.¹⁰

REFERENCES

1. Hulka JH. Bone conduction changes in acute otitis media. *Arch Otolaryngol* 1941;33:333-50.
2. Gardenghi G. Contributo allo studio della funzione cochleale nell'otite media purulenta cronica. *Boll Mal Orecch* 1955;73/6:587-606.
3. Bluushtein GM. Audiologicheskaya kharakteristika khronicheskikh gnoinykh srednikh ototou. *Vestn Otorinolaringol* 1963;25:64-72.
4. Paparella MM, Brady DR, Hoel R. Sensorineural hearing loss in chronic otitis media and mastoiditis. *Trans Am Acad Ophthalmol Otolaryngol* 1970;74:108-15.
5. English GM. Chronic otitis media as a cause of sensorineural hearing loss. *Arch Otolaryngol* 1973;98:18-22.
6. Paparella MM, Goycoolea MV, Meyerhoff WL. Inner ear pathology and otitis media. A review. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):249-53.
7. Aviel A, Ostfeld E. Acquired irreversible sensorineural hearing loss associated with otitis media with effusion. *Am J Otolaryngol* 1982;3:217-22.
8. Morizono T, Giebink GS, Paparella MM, Sikora MA, Shea DA. Sensorineural hearing loss in experimental purulent otitis media due to *S pneumoniae*. *Arch Otolaryngol* 1985;111:794-8.
9. Morizono T. Otological agents: ototoxicity in animal studies. *Ann Otol Rhinol Laryngol* 1988;97(suppl 131):28-30.
10. Morizono T, Smith R, Canafax D, Giebink GS, Sikora MA. Ototoxicity of topically applied drugs used in otitis media treatment. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. *Recent advances in otitis media*. Toronto, Canada: BC Decker, 1988:447-9.
11. Nelson JD. Management of chronic suppurative otitis media: a survey of practicing pediatricians. *Ann Otol Rhinol Laryngol* 1988;97(suppl 131):26-8.
12. Meyerhoff W, Morizono T, Wright C, Shaddock L, Shea D, Sikora M. Tympanostomy tubes and otic drops. *Laryngoscope* 1983;93:1022-7.
13. Wright C, Meyerhoff W. Ototoxicity of otic drops applied to the middle ear in the chinchilla. *Am J Otolaryngol* 1984;5:166-76.
14. Ikeda K, Morizono T. The preparation of acetic acid for use in otic drops and its effect on endocochlear potential and pH in inner ear fluid. *Am J Otolaryngol* 1989;10:382-5.
15. Nomura Y. Otological significance of the round window. In: Pfaltz CR, ed. *Advances in otorhinolaryngology*. Vol 33. Basel, Switzerland: S Karger, 1984:1-162.
16. Morizono T, Sikora MA. Compound action potential input-output decrement — effect of topically applied antiseptics. *Arch Otolaryngol* 1983;109:677-81.

ROUND WINDOW MEMBRANE PERMEABILITY DURING EXPERIMENTAL PURULENT OTITIS MEDIA: ALTERED CORTISPORIN OTOTOXICITY

KATSUHISA IKEDA, MD

TETSUO MORIZONO, MD

MINNEAPOLIS, MINNESOTA

Round window membrane (RWM) permeability is the most critical factor influencing cochlear function following otitis media. Because otic drops are frequently used during purulent otitis media (POM), we investigated RWM permeability and ototoxicity of Cortisporin otic suspension after inducing experimental POM. Unilateral POM was induced in eight chinchillas by inoculating type 7F *Streptococcus pneumoniae* into the right ears. Left ears were inoculated with phosphate-buffered saline (control). When POM resolved, the animals were divided into two groups. The round window niches of group 1 were covered with Cortisporin otic suspension. Compound action potentials were measured before and after drug application. The RWM permeability was measured in group 2 by use of tetraethylammonium (TEA) ions as tracers, and the arrival time of TEA and the slope of the potassium-selective microelectrode response were measured. Animals with otitis media exhibited less susceptibility to ototoxicity of Cortisporin otic suspension and reduced RWM permeability to the medium-sized molecule TEA.

KEY WORDS — cochlear function, otic drops, round window membrane.

INTRODUCTION

Numerous reports suggest that otitis media induces sensorineural hearing loss, presumably due to penetration of ototoxic substances such as bacteria, bacterial toxins, ototoxic drugs, and inflammatory mediators into the inner ear.¹⁻⁶ Round window membrane (RWM) permeability is a most critical factor influencing cochlear function following otitis media.⁷⁻⁹ However, there are only a few studies of RWM permeability changes in relation to otitis media. Goycoolea et al¹⁰ observed increased RWM permeability to tritiated albumin during the early stages of serous otitis media produced by eustachian tube obstruction, and later in this experimental condition, Schachern et al¹¹ reported decreased RWM permeability to horseradish peroxidase, and Nomura⁷ observed decreased cochlear damage following the application of neomycin to the RWM. We demonstrated that bacterial toxins, both endotoxin and staphylococcal exotoxin, increased RWM permeability and that serous otitis media decreased permeability.¹² Round window membrane permeability has not been studied during purulent otitis media. Because it is in this condition that otic drugs are frequently used, we investigated RWM permeability soon after completing systemic antimicrobial treatment of experimental purulent otitis media.

MATERIALS AND METHODS

Eight healthy chinchillas weighing 450 to 550 g were used. Each animal was anesthetized with ketamine hydrochloride (40 mg/kg), and body temperature was maintained at 37°C by use of a heat-

ing blanket throughout the experiments. Two series of experiments were performed. Unilateral purulent otitis media was produced in all chinchillas by inoculating log-phase type 7F *Streptococcus pneumoniae* (10 colony-forming units) into the cephalad right bulla with a 25-gauge needle, and the same volume of phosphate-buffered saline was inoculated into the left bulla, which served as a control. All animals received an intramuscular injection of penicillin G procaine (100,000 units/kg) every 24 hours for 7 days beginning 24 hours after bacterial inoculation. When purulent otitis media had resolved, as confirmed by both the presence of a normal type A tympanogram and the absence of middle ear effusion by otoscopic examination, the action potential (AP) responses were measured in one group of four animals.¹³ A closed acoustic system with a probe microphone was used to deliver and monitor asynchronous tone bursts (1-ms rise-fall time, 10-ms plateau) at 16, 12, 8, 4, 3, and 2 kHz with a maximum level of 70 dB sound pressure level (SPL). A fenestra was made in the bulla and a silver wire was placed either on the RWM or on the round window niche. The sound pressure level that elicited a 10- μ V AP was determined at each frequency by interpolation. Thereafter, the round window niche was covered with about 50 μ L of full-strength Cortisporin suspension, consisting of polymyxin B, neomycin, and hydrocortisone, and changes in the AP threshold were measured 24 hours later.

In the remaining four chinchillas with resolved unilateral purulent otitis media, RWM permeability was measured with a tracer of tetraethylammo-

From the Otitis Media Research Center and the Department of Otolaryngology, University of Minnesota Medical School, Minneapolis, Minnesota. Supported by National Institutes of Health/National Institute on Deafness and Other Communication Disorders. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota.

REPRINTS — Otitis Media Research Center, University of Minnesota, Box 396 UMHC, 420 Delaware St SE, Minneapolis, MN 55455.

TABLE 1. EFFECT OF PURULENT OTITIS MEDIA ON ACTION POTENTIAL THRESHOLD

Animal No.	Ear Tested	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	12 kHz	16 kHz
584	Inoculated ear	34.6	42.9	34.6	29.6	24.7	43.0	52.8
	Uninoculated ear	34.6	37.5	28.5	25.0	21.7	32.0	37.3
585	Inoculated ear	—	—	—	—	—	—	—
	Uninoculated ear	35.8	33.5	25.3	21.6	16.6	26.0	50.9
588	Inoculated ear	37.9	40.7	35.5	26.9	24.0	35.1	43.2
	Uninoculated ear	47.0	24.3	21.8	20.5	17.1	26.5	37.3
590	Inoculated ear	30.7	27.9	23.7	23.1	23.8	29.2	26.6
	Uninoculated ear	27.3	28.7	16.4	17.8	1.6	22.7	20.0

Data represent 10- μ V action potential thresholds in decibels sound pressure level. Dash indicates no action potential response.

nium (TEA) ions.¹² The contralateral normal ears served as controls. A small hole was made 2 mm from the ridge of the round window at the scala tympani of the basal turn. A single-barreled potassium-selective microelectrode was inserted into the hole, and a chemical bone was used to seal around the microelectrode. Then, 150 mmol/L TEA was applied to the RWM. Two parameters were selected for analyzing RWM permeability: time between the application of TEA to the RWM and the onset of potential change (arrival time), and slope of the potassium-selective microelectrode response. The results, expressed as means $\pm$ SD, were analyzed by Student's nonpaired *t* test, and *p* < .05 was defined as a significant difference.

RESULTS

In all animals, bacteria-inoculated ears showed sensorineural hearing loss that required a larger sound pressure to elicit a 10- μ V AP amplitude compared with control ears (Table 1). One of the four animals showed total deafness in the inoculated ear. Therefore, the effect of Cortisporin applied to the RWM on the hearing level of inoculated and uninoculated ears was examined in the remaining three animals. The difference between AP thresholds prior to and following the application of Cortisporin was measured. When no AP response was observed, the threshold was defined as 70 dB SPL. In all three animals, the AP threshold shift 24 hours following Cortisporin application decreased less in inoculated than in control ears (Table 2).

The arrival time of TEA in the inoculated ears was significantly longer (5.1 ± 1.1 minutes) than in uninoculated ears (3.0 ± 0.3 minutes). The slope

was greater in inoculated ears (19.2 ± 5.8 mV/min) than in control ears (31.6 ± 10.1 mV/min), but the difference between ears was not significant.

DISCUSSION

Using two tracers of RWM permeability, we observed that recovery from experimental pneumococcal otitis media was associated with reduced ototoxicity of ototoxic Cortisporin and reduced RWM permeability to the medium-sized molecule TEA. These effects may have been caused by one or more of the following: 1) increased thickness of the RWM, 2) increased components, such as collagen, in the middle layer of the RWM acting as a permeability barrier, or 3) changes of the charge barrier in the cell surface of the RWM. Total thickness of the RWM may principally determine the time of RWM penetration, whereas the size barrier may determine the quantity of penetration. Sahni et al¹⁴ observed a significant increase in RWM thickness in ears with otitis media compared with normal ears — a finding that led us to hypothesize that a thickened RWM in chronic otitis media may protect the cochlea from ototoxic agents. In the present study, the prolonged TEA arrival time in infected ears implies that purulent otitis media causes thickening of the RWM. Although the outer epithelial layer or the connective tissue layer of the RWM are likely candidates for a filter with a size-limiting nature,^{8,11} the anatomic sites responsible for the permeability selectivity of the RWM are still controversial.

Goycoolea et al⁸ described the effect of molecular charge on RWM permeability. The cell surface is known to possess anionic macromolecules.¹⁵ Consequently, cationic molecules pass easily through the RWM. In contrast, anionic molecules are expected

TABLE 2. CHANGES OF ACTION POTENTIAL THRESHOLD DUE TO CORTISPORIN APPLICATION TO ROUND WINDOW MEMBRANE

Animal No.	Ear Tested	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	12 kHz	16 kHz
584	Inoculated ear	3.5	-12.0	6.2	11.3	10.3	9.0	-4.3
	Uninoculated ear	35.4	32.5	41.5	45.0	48.3	38.0	32.7
588	Inoculated ear	24.0	6.2	13.2	22.0	28.1	34.9	26.8
	Uninoculated ear	23.0	45.7	47.2	49.5	52.9	43.5	32.7
590	Inoculated ear	8.1	7.3	12.4	3.7	5.1	17.0	26.5
	Uninoculated ear	42.7	41.3	53.6	52.2	68.4	47.3	50.0

Data represent 10- μ V action potential thresholds in decibels sound pressure level.

to encounter forces of repulsion from a negatively charged cell coat. However, the cell membrane's electrical charge may be neutralized during middle ear inflammation by cationic substances such as neutrophil lysosomes¹⁶ and chemical mediators. The decrease in RWM anionic charge may prevent cationic molecules such as polymyxin B, neomycin,

and TEA from entering the RWM.

Further experiments are necessary to elucidate the effect of pneumococcal otitis media on RWM permeability, and to test the ototoxicity of different ototopical preparations in ears with various types of otitis media.

REFERENCES

1. Paparella MM, Morizono T, Le CT, et al. Sensorineural hearing loss in otitis media. *Ann Otol Rhinol Laryngol* 1984;93: 623-9.
2. Moore DC, Best GF. A sensorineural component in chronic otitis media. *Laryngoscope* 1980;90:1360-6.
3. Morizono T, Johnstone BM. Ototoxicity of topically applied gentamicin using a statistical analysis of electrophysiological measurement. *Acta Otolaryngol (Stockh)* 1975;80:389-93.
4. Morizono T, Giebink GS, Paparella MM, Sikora MA, Shea D. Sensorineural hearing loss in experimental purulent otitis media due to *Streptococcus pneumoniae*. *Arch Otolaryngol* 1985; 111:794-8.
5. Kawauchi H, DeMaria TF, Lim DJ. Endotoxin permeability through the round window. *Abstr Assoc Res Otolaryngol* 1988;184.
6. Lundman L, Juhn SK, Morizono T, Santi PA. *Pseudomonas aeruginosa* exotoxin A: effect on the inner ear and its passage through the round window membrane [Abstract]. *Otolaryngol Head Neck Surg* 1988;99:171.
7. Nomura Y. Otological significance of the round window. In: Pfaltz CR, ed. *Advances in otorhinolaryngology*. Vol 33. Basel, Switzerland: S Karger, 1984:1-162.
8. Goycoolea MV, Muchow D, Schachern PA. Experimental studies on round window structure: function and permeability. *Laryngoscope* 1988;98(suppl 44).
9. Goycoolea MV, Paparella MM, Juhn SK, Carpenter A-M. Oval and round window changes in otitis media: potential pathways between middle ear and inner ear. *Laryngoscope* 1980;90: 1387-91.
10. Goycoolea MV, Paparella MM, Goldberg V, Carpenter A-M. Permeability of the round window membrane in otitis media. *Arch Otolaryngol* 1980;106:430-3.
11. Schachern PA, Paparella MM, Goycoolea MV, Duvall AJ, Choo YB. The permeability of the round window membrane during otitis media. *Arch Otolaryngol Head Neck Surg* 1987;113: 625-9.
12. Ikeda K, Morizono T. Changes of the permeability of round window membrane in otitis media. *Arch Otolaryngol Head Neck Surg* 1988;114:895-7.
13. Morizono T, Sikora MA. The ototoxicity of topically applied povidone-iodine preparations. *Arch Otolaryngol* 1982;108: 210-3.
14. Sahni RS, Paparella MM, Schachern PA, Goycoolea MV, Le CT. Thickness of the human round window membrane in different forms of otitis media. *Arch Otolaryngol Head Neck Surg* 1987;113:630-4.
15. Seno S. Ionized groups on the cell surface. Their cytochemical detection and related cell function. *Int Rev Cytol* 1987;100: 203-48.
16. Ryan GB, Majno G. Acute inflammation. *Am J Pathol* 1977;86:184-276.

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**WORKSHOP ON EPIDEMIOLOGY OF
OTITIS MEDIA**

Editors

CHARLES D. BLUESTONE, MD

MARGARETHA L. CASSELBRANT, MD, PhD

Associate Editor

MARY D. SCHEETZ, MLS

ANNALS
OF OTOTOLOGY,
RHINOLOGY &
LARYNGOLOGY

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Associate Editor

MARY D. SCHEETZ, MLS

Additional copies of this publication are available from Charles D. Bluestone, MD, Dept of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, 3705 Fifth Ave at DeSoto St, Pittsburgh, PA 15213-2583, or may be purchased from Annals Publishing Company, 4507 Laclede Ave, St Louis, MO 63108.

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PARTICIPANTS

Charles D. Bluestone, MD
Professor of Otolaryngology
University of Pittsburgh School of Medicine
Director, Department of Pediatric Otolaryngology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

David Canterbury, EdD
Director, Communicative Disorders Program
Alaska Department of Health
Anchorage, Alaska

Margaretha L. Casselbrant, MD, PhD
Research Assistant Professor of Otolaryngology
University of Pittsburgh School of Medicine
Director, Clinical Research
Department of Pediatric Otolaryngology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Helen B. Craig, PhD
Research Director
Western Pennsylvania School for the Deaf
Pittsburgh, Pennsylvania

Gregory Dever, MD
Department of Pediatrics
University of Hawaii at Manoa
John A. Burns School of Medicine
Kapiolani-Children's Medical Center
Honolulu, Hawaii

Philip Fireman, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Director, Allergy, Immunology and Rheumatology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Phillip H. Kaleida, MD
Associate Professor of Pediatrics
University of Pittsburgh School of Medicine
Associate Director, Ambulatory-Community
Pediatrics Fellowship
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Margaret A. Kenna, MD
Assistant Professor, Surgery (Otolaryngology) and Pediatrics
Department of Surgery
Yale University School of Medicine
New Haven, Connecticut

Jerome O. Klein, MD
Professor, Pediatrics
Boston University School of Medicine
Director, Division of Pediatric Infectious Diseases
Maxwell Finland Laboratory for Infectious Disease
Boston City Hospital
Boston, Massachusetts

Michael S. Kramer, MD
Department of Epidemiology and Biostatistics
McGill University School of Medicine
Montreal, Quebec, Canada

Kaj Lundgren, MD
Department of Oto-Rhino-Laryngology
Malmö General Hospital
Malmö, Sweden

Ellen M. Mandel, MD
Assistant Professor of Pediatrics
University of Pittsburgh School of Medicine
Clinical Research Pediatrician
Department of Otolaryngology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Colin D. Marchant, MD
Head, Department of Pediatrics
St Boniface General Hospital
Winnipeg, Manitoba, Canada

John D. Nelson, MD
Professor, Pediatrics
University of Texas
Southwestern Medical School
Health Science Center
Dallas, Texas

Robert J. Nozza, PhD
Assistant Professor of Otolaryngology
University of Pittsburgh School of Medicine
Director of Audiology, Division of Audiology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Jack L. Paradise, MD
Professor, Pediatric Community Medicine
University of Pittsburgh School of Medicine
Director, Ambulatory Care Center
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Juhani Pukander, MD
Assistant Professor of Otolaryngology
Department of Clinical Sciences
University of Tampere
Tampere, Finland

Howard E. Rockette, PhD
Professor of Biostatistics
University of Pittsburgh
Graduate School of Public Health
Pittsburgh, Pennsylvania

Paul A. Shurin, MD
Department of Clinical Investigation
American Cyanamid Co
Lederle Labs
Pearl River, New York

Joseph L. Stewart, PhD
Indian Health Service
Sensory Disabilities Program
Albuquerque, New Mexico

Sylvan E. Stool, MD
Professor of Pediatrics and Otolaryngology
University of Pittsburgh School of Medicine
Director of Education
Department of Otolaryngology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Tomonori Takasaka, MD
Professor and Chairman
Department of Otolaryngology
Tohoku University School of Medicine
Sendai, Miyagi-Ken, Japan

Norman Wendell Todd, Jr, MD
Assistant Professor
Emory University
Division of Otolaryngology
Emory University Clinic
Atlanta, Georgia

Mirko Tos, MD
Professor and Chairman
Department of Otolaryngology
University of Copenhagen
Gentofte Hospital
Hellerup, Denmark

Ellen R. Wald, MD
Associate Professor, Pediatrics
University of Pittsburgh School of Medicine
Director, House Staff Training
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

George W. Williams, PhD
Division of Research
Chairman, Department of Biostatistics and Epidemiology
Cleveland Clinic Foundation
Cleveland, Ohio

INTRODUCTION

The Workshop on Epidemiology of Otitis Media was held in Pittsburgh, Pennsylvania, on Aug 28 and 29, 1986, as part of an ongoing series sponsored by the Pittsburgh Otitis Media Research Center of Children's Hospital of Pittsburgh (OMRC).¹⁻⁶ The OMRC is funded in part by a grant from the National Institutes of Health (DC00158).

Studies related to epidemiology of otitis media have increased significantly during the past decade because of the growing interest of investigators from around the world. Information derived from these studies is important in understanding the etiology and pathogenesis of otitis media and can aid in improving the management and prevention of this common disease. The purpose of this Workshop was to bring together experts from many countries to present their studies of the epidemiology of otitis media, to discuss their findings, and to identify areas for future research.

We are indebted to Beecham Laboratories, Bristol, Tennessee, for their financial support of this Workshop and for the publication of the proceedings.

Charles D. Bluestone, MD
Margaretha L. Casselbrant, MD, PhD

REFERENCES

1. Bluestone CD, Cantekin EI, Diven WF, et al. Effects of antimicrobial agents on the biological activity of the middle ear with otitis media. *Ann Otol Rhinol Laryngol* 1983;92(suppl 107):48-50.
2. Bluestone CD, Klein JO, Paradise JL, eds. Workshop on effects of otitis media on the child. *Pediatrics* 1983;71:639-52.
3. Bluestone CD, Klein JO. Controversies in antimicrobial agents for otitis media. Introduction: goals and definitions. *Pediatr Ann* 1984;13:361-3.
4. Bluestone CD, Doyle WJ, eds. Eustachian tube function: physiology and role in otitis media. Workshop report. *Ann Otol Rhinol Laryngol* 1985;94(suppl 120).
5. Bluestone CD, Fria TJ, Arjona SK, et al. Controversies in screening for middle ear disease and hearing loss in children. *Pediatrics* 1986;77:57-60.
6. Bluestone CD, Klein JO, eds. Proceedings of a workshop on vaccines for otitis media. *Pediatr Infect Dis J* 1989;8:S1-S97.

METHODOLOGY

ISSUES IN DISEASE IDENTIFICATION

MICHAEL S. KRAMER, MD

INTRODUCTION

A disease can be defined as any symptom, sign, or laboratory finding that, either singly or in combination, leads to mortality, morbidity, or impaired performance. In other words, it is a condition that persons are better off without. Diseases are best identified by means of some accepted "gold standard." In the case of otitis media, the best gold standard is probably the clear pathologic demonstration of inflammation of the tympanic membrane or other middle ear structures. But because such a demonstration requires biopsy or autopsy, a next-best gold standard has been achieved by examination of middle ear fluid obtained at myringotomy.^{1,2}

Unfortunately, use of an invasive examination or test such as myringotomy is an unacceptable and impractical way for clinicians or clinical investigators routinely to identify persons with a disease. Rather, they usually rely on symptoms, signs, or laboratory results that presumably correspond fairly closely to the gold standard. In this paper, I would like to show how these clinical findings can be used to identify diseases in general, using otitis media as an illustrative example. For the sake of simplicity, I will refer to all of them as diagnostic markers or tests.

VALIDITY OF DIAGNOSTIC MARKERS

Most diagnostic markers consist of either the measurement of a single continuous variable, such as serum thyroxine or systolic blood pressure, or a list of clinical criteria. Yet the results are interpreted dichotomously, that is, positive versus negative, diseased versus disease free. This means that so-called normal limits must be established. But since there is almost always some overlap in values between the true diseased and disease-free populations, any cutoff point chosen to define these normal limits will result in errors in classification.

The ability of a diagnostic marker to identify a disease correctly is known as its validity. Validity is usually assessed in a group of patients in whom results are available for both the diagnostic marker and the gold standard. Validity is evaluated conditionally, that is, separately, in those subjects with and without the disease. The proportion of correctly identified diseased subjects is called the sensitivity, and the corresponding proportion of those who are disease free is called the specificity.³

Sensitivity and specificity can be derived easily from a standard 2 x 2 table (Table 1). Disease presence and absence constitute the column headings, and test positivity and negativity form the rows. The a is the number of subjects with the disease and a positive test result, the so-called true positives (TPs). Similarly, b is the number of false positives (FPs); c, the false negatives (FNs); and d, the true negatives (TNs). Sensitivity is defined as the proportion of diseased subjects with a positive test result, that is, TP over TP plus FN, or $\frac{a}{a+c}$. Specificity is the proportion of disease-free subjects with a negative test result, or TN over TN plus FP, or $\frac{d}{d+b}$.

The perfectly valid diagnostic marker would have a sensitivity and specificity both equal to 1. But because the distribution of results in the diseased and disease-free populations overlaps, any shift in the chosen cutoff point that increases the proportion of diseased subjects identified will decrease the proportion classified correctly as disease free. In other words, the greater we make the sensitivity, the lower will be the specificity and vice versa.

This reciprocal relationship between sensitivity and specificity can be represented by the receiver operating characteristics (ROC) curve (Fig 1). Here sensitivity is graphed on the y-axis and 1 - specificity on the x-axis. The greater the sensitivity, the lower the specificity and vice versa. Different points on the ROC curve represent different choices of cutoff points. A represents a point on the curve that results in a specificity of 1 but a sensitivity of only 0.3. At the other extreme, D represents a sensitivity of 1 but a specificity of only 0.2. B and C are intermediate points. The choice of which of these cutoff points is most appropriate for a diagnostic marker should be governed by the purpose for which it is obtained.⁴ If sensitivity is important, a point on the curve near C or D is appropriate. When specificity is more important, A or B would be preferable.

It is thus the curve itself rather than a specific point that is characteristic of the test; no one point on the curve makes the test better or worse. A better test, ie, one with better overall sensitivity and specificity, would have an ROC curve that lies above and to the left of the curve shown in Fig 1. In fact, the position of the curve with respect to the diagonal dashed line is an indicator of its informational value. The diagonal represents the line for which sensitivity = 1 - specificity, ie, sensitivity + specificity = 1. A test for which sensitivity and specificity sum to 1 contributes no more information than pure chance. The closer the ROC curve lies to the diagonal, the less information it provides; the further above and to the left of the diagonal, the more informative it is.

SPECTRUM AND BIAS IN EVALUATION STUDIES

Adequate assessment of a test's sensitivity and specificity depends on the proper design of evaluation studies.⁵ A wide spectrum of cases, or persons with the disease, is re-

TABLE 1. EVALUATION OF DIAGNOSTIC MARKERS

Test	Disease	
	Present	Absent
Positive	a	b
Negative	c	d
Sensitivity = $\frac{TP}{TP + FN} = \frac{a}{a + c}$, specificity = $\frac{TN}{TN + FP} = \frac{d}{d + b}$, positive predictive value = $\frac{TP}{TP + FP} = \frac{a}{a + b}$, and negative predictive value = $\frac{TN}{TN + FN} = \frac{d}{d + c}$.		

a — true positive (TP), b — false positive (FP), c — false negative (FN), d — true negative (TN).

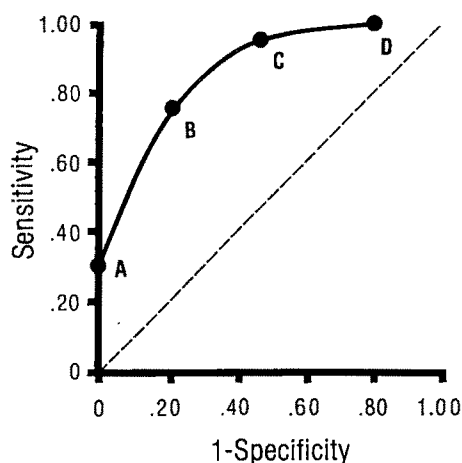


Fig 1. Receiver operating characteristics (ROC) curve.

quired to assess the sensitivity of the test adequately. Of particular importance is the severity of disease. In an attempt to avoid misclassification, many investigators evaluating a new test will study only cases of severe, advanced disease. When the test is later administered by other clinicians and investigators to subjects with much milder forms of the disease, many more FNs will occur and thus the test's sensitivity will be far lower. For otitis media, the sensitivity of otoscopic or tympanometric findings is likely to be reduced considerably when applied to a general patient population, even one with symptoms compatible with otitis media, than it is in a group of patients with advanced middle ear disease referred for tympanostomy tube placement.

A broad spectrum of disease-free control subjects is necessary for the adequate assessment of a test's specificity. Most investigators evaluating a new test will choose healthy, asymptomatic normal persons as a control group to minimize the possibility of misclassification. Very few such persons have a positive test result, but when the test then is applied in the real world of sick, symptomatic patients, more FPs occur and the specificity deteriorates accordingly. This probably has not been a problem for diagnostic markers of otitis media.

The other main type of defect in design of diagnostic marker studies is bias. Bias can affect both sensitivity and specificity and is particularly likely to occur when the test involves some subjective judgment and the tester is aware of the results of the gold standard. Blinding of the tester provides an adequate safeguard against such bias, and blinding has been employed in several studies evaluating otoscopic and tympanometric criteria for otitis media.

PREDICTIVE VALUE AND USE OF BAYES' THEOREM

The statistical indices of sensitivity and specificity are extremely useful in assessing the validity and informational value of a diagnostic marker, but they have a major drawback for clinicians, because the reasoning upon which they are based is backward from diagnostic reasoning. Sensitivity and specificity start from subjects with and without the disease and determine how often the test result is either positive or negative, respectively. Unfortunately, a clinician's patients usually do not come to him already bearing labels indicating "diseased" or "disease free." Instead, the clinician begins with a test result and then must decide whether the patient has or does not have the dis-

ease. Clinicians are interested, therefore, in a test's predictive value.^{3,6}

As shown in Table 1, positive predictive value is defined as the proportion of subjects with a positive test result who have the disease, that is, TP over TP plus FP, or $\frac{a}{a+b}$. Negative predictive value is the proportion of subjects with a negative test who are disease free, that is, TN over TN plus FN, or $\frac{d}{d+c}$.

Unlike sensitivity and specificity, positive and negative predictive values are not true indices of validity, because they depend on the relative proportion of diseased and disease-free persons being tested. Suppose a new test has been developed to detect middle ear effusion. The developers of the test evaluate its validity using 100 patients with proven effusion and 100 control subjects, and the test performs very well: sensitivity is 95/100, or 0.95. Specificity is 85/100, or 0.85. Positive predictive value is 95/110, or 0.86, and negative predictive value is 85/90, or 0.94. The test is then hailed as a major breakthrough and the authors of the resulting article urge its use to screen healthy schoolchildren for middle ear effusion.

Let us assume that the prevalence of middle ear effusion in healthy schoolchildren is 20 per 1,000, or 2%. When the first 1,000 children are screened, the sensitivity and specificity remain constant at 0.95 and 0.85, respectively. Negative predictive value is extremely high at 0.999. But the positive predictive value plummets to

$$\frac{(0.95)(20)}{(0.95)(20) + (0.15)(980)} = 19/166, \text{ or } 0.11.$$

In other words, of every 9 children with a positive test, only 1 actually will turn out to have an effusion. This originally promising test certainly looks far less so now, at least in terms of its usefulness for screening purposes.

Thomas Bayes was an 18th-century clergyman and mathematician interested in conditional probability, that is, the probability that an event would occur under a given condition. Although identification of disease was far from Bayes' mind at the time, the theorem that bears his name has proved useful for determining the positive predictive value of diagnostic markers:

$$P(D|T^+) = \frac{P(T^+|D) \cdot P(D)}{P(T^+)}$$

In other words, the probability of disease given a positive test result is the product of the probability of a positive test result given disease, times the probability of disease, divided by the probability of a positive test result.

Each of the four components in this formula can be made easily recognizable. As we have already seen, $P(D|T^+)$ is the positive predictive value of the test. Bayesians often refer to it as the posterior, or posttest, probability of disease, because it is known only after the test result is known. $P(T^+|D)$ is also familiar to us already as sensitivity. Sensitivity is the proportion of diseased subjects with a positive test result, which is exactly the same thing as the probability of a positive test result given disease. The third component, $P(D)$, is called the prior, or pretest, probability of disease, because it is the probability that the subject has the disease before the test result is known. We use everything we know about the subject prior to the test to arrive at this probability. If we know nothing about the subject other than the population group from which he or she comes, $P(D)$ is the same as the prevalence of the disease in that population. Thus, as we saw earlier, disease preva-

lence is one of the determinants of positive predictive value. The fourth and last component in the formula, $P(T^+)$, is the total probability of getting a positive test result, including both persons with and without the disease, that is, TPs and FPs.

Bayes' theorem can also be used to calculate the probability that a subject will be disease free, which we can represent by $\bar{D}$:

$$P(\bar{D}|T^+) = \frac{P(T^+|\bar{D}) \cdot P(\bar{D})}{P(T^+)}$$

Although $P(\bar{D}|T^+)$ may be of some interest to clinicians in its own right, this formula allows Bayes' theorem to be expressed in terms of odds. The term odds means merely the ratio of a probability to its complement, ie, 1 minus that probability. If we divide the first formula by the second, we obtain a third [(the two $P(T^+)$ terms cancel out)]:

$$\frac{P(D|T^+)}{P(\bar{D}|T^+)} = \frac{P(T^+|D)}{P(T^+|\bar{D})} \cdot \frac{P(D)}{P(\bar{D})}$$

This third formula says that the odds of disease given a positive test result (which is also called the posterior odds) is the product of the odds of a positive test result under the competing alternatives of disease and nondisease (which is known as the likelihood ratio) multiplied by the relative proportion of diseased and disease-free subjects tested, that is, the prior odds. In other words, the posterior odds equals the likelihood ratio times the prior odds.

It can be seen further that the likelihood ratio is nothing

more than the ratio of sensitivity to $1 - \text{specificity}$, since the denominator is the proportion of FPs among the disease free. Stating Bayes' theorem in terms of odds thus provides an instant index of the informational value of a positive test result. Of the two terms on the right side of the equation, the test contributes only to the first one, that is, the likelihood ratio. If the test conveys no new information, ie, if the likelihood ratio equals 1, the posterior odds and the prior odds are the same. Consequently, the test result does not change the probability that the subject has the disease. If the likelihood ratio equals 1, then sensitivity = $1 - \text{specificity}$ and sensitivity + specificity = 1. This is exactly the same situation as that represented by the diagonal line in the ROC curve (Fig 1). A test whose sensitivity and specificity sum to 1 is useless.

CONCLUSION

There is probably no such thing as a diagnostic marker that enables perfect identification of a disease. But it is also true that some markers are better than others, and there is no question that recent advances in technology and clinical research have greatly improved our ability to identify a number of disease entities. My main message is that tests make better slaves than masters. Adequate attention to sensitivity and specificity, to the design of studies in which sensitivity and specificity are evaluated, and to disease prevalence and predictive value will help ensure the accurate identification of disease and the efficient use of our limited health care resources.

ANALYSIS OF REPEATED MEASURES ON THE SAME OR MATCHED EXPERIMENTAL UNIT(S) IN MEDICAL RESEARCH

GEORGE W. WILLIAMS, PHD

Repeated measurements on the same experimental unit or matched experimental units occur frequently in medical research. This situation may arise by the measurement of multiple sites on the same patient, measurements on twins, or measurements on matched control subjects. The efficiency of such designs can be great, although care must be exercised in the choice of design for any specific research project. Frequently, the design of the study is ignored in the analysis of the resulting data, eg, applying analyses appropriate only for unpaired designs. Repeated measurements made in the course of a longitudinal study also lead to correlation among subjects' measurements that should be considered in a proper analysis. Errors can arise when multiple observations on subjects are analyzed as though they represent single observations from distinct subjects. The effect of this error on the inferences made depends upon the specific design and analysis of the study. Various analytic techniques exist to avoid these errors.

Pairs of experimental units can arise in various ways in medical research. Self-pairing arises when the same experimental unit, eg, individual, belongs to both comparison groups. Humans and animals have pairs of arms, legs, eyes, and ears. The application of one procedure or treatment to one arm, leg, eye, or ear of a patient while another procedure is applied to the other arm, leg, eye, or ear defines a self-pairing situation.⁷ A further example of a self-paired situation is a crossover design in which some variable is measured before and after a particular therapy on the same person.⁸ The advantage of within-patient

comparison of treatments is that usually far fewer cases are needed than in a design that calls for patients to be randomized to receive one treatment or another. Within-patient comparisons of treatments should be avoided, however, when treatments can act systemically or when there is the possibility of contamination between treatment areas.⁹ Other naturally occurring pairs include twins. In animal experimentation, littermates often provide the experimental material. Experimental units can be matched with respect to a series of extrinsic variables, eg, a case-control study. As opposed to individually matched pairs, matched samples can be created by the use of frequency matching.¹⁰

Care must be exercised in the analysis of data arising from a paired design. For example, the fact that procedures are carried out on the same patient invalidates the usual χ^2 test for comparing, say, the rate of success for the various procedures. This is due to the basic assumption of the usual χ^2 test that the observations in the contingency table must be independent. McNemar,¹¹ however, proposed a procedure for testing the hypothesis of no association for such data. In order to carry out this test, the data must be cast to count each patient only once. Extensions of this test to more than dichotomous data are available, eg, Cochran's Q.¹² Depending upon the distributional properties of the variables being analyzed, alternative test statistics are available. For Gaussian or normally distributed random variables, a paired test based on differences for each pair would be used to compare mean values. Non-

parametric procedures such as the Wilcoxon signed ranks test and the sign test are available. Interest is not always in a test of significance, and sometimes estimates of treatment differences along with their corresponding confidence limits are more appropriate. Many standard textbooks provide the details of the various computations.¹³⁻¹⁵

Appropriate statistical procedures are available when comparisons are made among three or more sets of matched observations. For example, paired *t* tests generalize to analysis of variance procedures. Nonparametric tests generalize as well, eg, Friedman's test. Fleiss¹³ discusses analysis of categorical data in the case of multiple samples as well as multiple controls. Incomplete randomized block designs and associated analysis of variance procedures compare data from *k* treatments in blocks of size *r*, with *r* smaller than *k*.¹⁶ Nonparametric counterparts for the analysis of incomplete block designs are also available.¹⁷ Multiple comparison procedures are available to examine individual contrasts among groups. In the case of small sample sizes and categorical data, exact binomial procedures and conditional maximum likelihood approaches are available.¹⁸

Disregard of the pairing in the analysis of the results of a paired experiment represents a major pitfall to medical investigators. Often, however, the inappropriate analysis of paired data as if they were from independent samples will not lead to any conclusions materially different from those obtained with the proper paired analysis.¹⁷

Another common study design in the medical literature entails recording serial measurements of the same variable(s) on the same subject at several points in time. Because repeated observations are made on each subject, correlation is anticipated among a subject's measurements. This correlation must be accounted for to obtain a correct statistical analysis. When the outcome variable is approximately Gaussian, a large class of models is available for analysis. Univariate approaches include the analysis of some characteristic of the subject's profile, such as the time taken to reach a peak or the length of time above a given level. Multivariate generalizations of the paired *t* test, namely, Hotelling's paired *T*², are available. For multiple samples, the profile analyses described by Morrison¹⁹ can examine response by group interaction, response effects, and group effects. These techniques assume that observations are drawn from multivariate normal distributions with common but unrestricted covariance structure. In some longitudinal studies, it is not possible to fully control the circumstances under which the measurements are taken, and there may be considerable variation among investigators in the number and timing of observations. The resulting unbalanced data sets are typically not amenable to analysis using a general multivariate model with unrestricted covariance structure.²⁰ Moreover, additional difficulties occur when a repeated measures design employs several outcome variables. In this situation, inclusion of the within-subjects factor would multiply the length of the outcome vector for each subject by the number of levels of the within-subjects factor, eg, time points, and often would bring the total number of variables in the outcome vector close to the total number of subjects, thereby producing a very small number of degrees of freedom.²¹

Grizzle and Allen,²² Rao,²³ and Hui²⁴ have discussed methods based on fitting growth curves to the repeated ob-

servations for each subject. Here, each subject's data are modeled as a function of time, and the dependence of the resulting coefficients on the covariates then is assessed. Laird and Ware²⁰ developed random-effects models in which repeated observations for a subject are assumed to share a common random component. Azzalini²⁵ discussed models in which autoregressive error structure was assumed, and Ware²⁶ has presented an overview of linear models for Gaussian longitudinal data.

Techniques also exist when the outcome is not Gaussian. Random-effects models for binary outcomes have been developed. Stiratelli et al²⁷ and Anderson and Aitkin²⁸ have developed a logistic model; Ochi and Prentice,²⁹ a probit model; and Koch et al,³⁰ log-linear models. Cox³¹ suggested a logistic regression model for the conditional expectation of binary data, given previous observations. Zeger and Liang³² have recently proposed a unified approach to the analysis of longitudinal data for discrete and continuous outcomes.

As opposed to paired designs and longitudinal studies, repeated measurements sometimes are made on the same experimental unit at the same time under the same experimental conditions. Errors result when an investigator analyzes multiple observations on one such unit (or patient) as though these observations represent single observations from distinct patients. Repeat observations vary less than independent assessments. It is then impossible to draw inferences from analyses relying on statistically independent observations. For example, dental studies of caries activity frequently include the measurement of such activity on individual teeth. Analysis of data collected on individual teeth by usual statistical procedures may be difficult if not impossible to interpret, since the tooth is not the actual sampling unit. If a person enters the study, then all his or her teeth enter the study, and it cannot be assumed that the status for two adjacent teeth in the same mouth is as unrelated as the status for two teeth, one each from different mouths. In other words, teeth cluster together by the mouthful, and thus the independence assumption necessary for such statistical tests as the usual χ^2 test and most other procedures is violated. To avoid this difficulty, we must be sure that the contingency table shows counts of people, the basic sampling unit. For example, people could be classified according to whether they had no decayed, missing, or filled (DMF) teeth, exactly one DMF tooth, exactly two DMF teeth, or more than two DMF teeth. Alternatively, if a particular tooth, such as the lower right first molar, is defined as an indicator, an individual could be classified as to whether the indicator tooth was a DMF tooth or not.³³

In ophthalmologic studies, the fundamental unit for statistical analysis is often the eye rather than the person. Frequently, descriptive statistics are computed over distributions of eyes, and tests of hypotheses are constructed to compare such distributions. If the purpose is to compare two different types of people, then a person contributes two eyes' worth of information to such an analysis. Rosner^{34,35} shows that frequently used methods of analysis when each eye is treated as an independent random variable are shown to be invalid in the presence of intraclass correlation. They yield true *p* values two to six times as large as nominal *p* values when realistic assumptions are made about the degree of correlation between eyes. His results may be applicable to the analysis of data from other areas of medicine such as otolaryngology, when highly

correlated observations are obtained from two ears of a person and it is desirable to use all the information in the analysis.

Alternative analysis procedures include performing separate analyses for left and right eyes or representing all variables on a person-specific basis and performing standard statistical analysis.³⁶ These approaches are valid but may be inefficient. For example, it is possible that analyses of separate eyes would yield nonsignificant results (or one eye-specific analysis would yield significant results while the other would not), while an analysis appropriately combining evidence over individual eyes would result in overall significant results. Moreover, person-specific analyses do not allow the analysis of the relationship of outcome to predictor variables at the eye-specific level. It should be noted that if the correlation between eyes is highly positive, then an analysis of, for example, the left eye may be sufficient, since the second eye adds little information. The use of a summary person-specific measure such as the largest or smallest of a series of measurements on a person would be misleading if the number of repeated observations varied widely among individuals.

As a final example of statistical issues involved in the analysis of repeated measurements on the same experimental unit, let us consider the case of linear regression. To in-

crease sample size, an investigator might take several pairs of measurements (x , y) on the same subject, followed by a regression analysis in which measurements over all subjects are combined. Violation of the assumption of independent observations undermines the validity of the significance of tests involving both the slope parameter and the intercept parameter. The ordinary least squares (OLS) estimators remain unbiased, but they are no longer fully efficient. This loss in efficiency, however, is not the greatest damage to OLS procedures caused by the presence of this correlation. A more serious problem is that the estimated variances of the OLS estimators may be severely biased. In some cases, the true standard error of the estimated slope may be underestimated by the usual standard error, and the observed p value for the test of whether the slope is zero will underestimate the correct p value. In other cases, the usual standard error of the estimated slope will be overestimated, and hence the p value for the significance test of the slope will be biased upward. Thus, a significant relationship between y and x as inferred from the usual analysis will, in fact, be even more significant. Two methods that take into account this correlation include 1) adjustment of the standard errors computed from the OLS analysis and 2) direct application of generalized least squares.³⁷ A general discussion of regression analysis with omitted covariates has been presented by Gail et al.³⁸

DESIGN CONSIDERATIONS IN STUDIES OF OTITIS MEDIA

HOWARD E. ROCKETTE, PhD

The purpose of this paper is to address some of the issues that should be considered in designing studies of otitis media. It is impossible to cover all aspects of design in a short presentation, so we will restrict ourselves to the following: 1) definition of disease, 2) definition of outcome, 3) type of study design, 4) confounding variables, and 5) sample size estimates.

Much controversy still remains relative to the definition of disease in otitis media.^{39,40} The literature addresses several different manifestations of disease, including chronic otitis media with effusion, otitis media with effusion, and acute otitis media. Our purpose is not to standardize definitions, but to demonstrate the extent to which an ambiguous definition can impact on the patient population X considered eligible for a study. As an example, consider studies of acute otitis media with effusion. In a recently completed study at the OMRC at Children's Hospital of Pittsburgh, patients were entered if they had either signs or symptoms of acute otitis media with effusion. A sign of acute otitis media with effusion was defined to be erythema and/or white opacification (other than scarring) of the tympanic membrane, accompanied by fullness or bulging and impaired mobility of the membrane. The symptoms of acute otitis media with effusion for this study were otalgia, irritability, and fever. All children were evaluated by a validated otoscopist. The two medical centers participating in this study have different patient distributions, as determined by the presence of signs and symptoms (Table 2). This difference may result because the patient populations at the two clinics are different, or it may be a result of differing clinical judgment in the application of the criteria for acute otitis media with effusion. If the eligibility criteria had not been clearly

specified and documented, these differences in patient characteristics at the two clinics could not be addressed in the analysis. Since the information has been obtained, we are able to investigate (when sample size is sufficiently large) whether individual characteristics that make up the definition are prognostic and whether they are related to treatment efficacy. In addition, we obtain information that will enable us to assess the representativeness of our population better when making comparisons to other research studies.

A second problem encountered in investigating otitis media is the definition of outcome. A review of the literature indicates a variety of outcome measures that are used in studies of otitis media. These include presence of otitis media with effusion at a specific point in time, percentage of time with effusion, number of occurrences of otitis media with effusion, number of new acute episodes of otitis media with effusion, and time to recurrence of disease. Each of these variables is a valid measurement relative to the study of otitis media, and each has its own clinical significance. In designing a study one should be specific with regard to the primary end point. Failure to identify the primary outcome during the design phase may result in

TABLE 2. DISTRIBUTION OF SIGNS AND SYMPTOMS OF ACUTE OTITIS MEDIA WITH EFFUSION BY CLINIC

Clinical Condition	Site 1		Site 2	
	No. Pts	%	No. Pts	%
Signs and symptoms	121	73.3	152	41.0
Signs only	2	1.2	58	15.6
Symptoms only	42	25.4	161	43.4
Total	165		371	

TABLE 3. RELATIONSHIP OF AGE AND OTITIS MEDIA WITH EFFUSION AT 2 WEEKS

Age (yr)	OME Placebo			AOME Placebo		
	Effusion-Free No.	Relative %	Risk	Effusion-Free No.	Relative %	Risk
<2	104	12.5	.95	108	29.6	.65*
2-5	166	13.3	1.05	85	38.8	1.05
>6	78	12.8	.99	25	68.0	2.02†

OME — otitis media with effusion, AOME — acute otitis media with effusion.
 *Significant at $p < .05$.
 †Significant at $p < .01$.

many post hoc tests that if selected for presentation on the basis of a low significance level will elevate the type I error, ie, the chance of a false-positive finding.⁴¹ Secondary questions may be addressed in the analysis, but they should be interpreted with the appropriate caution in dealing with multiple comparisons.

The specific study design selected has an impact on the type of analysis that will be necessary and the cost of conducting the study. Since each specific study design has advantages and disadvantages, the selection of the most appropriate design requires careful consideration. Studies in which patients serve as their own controls are efficient in that they require fewer patients, but they must be used cautiously, since they require a greater number of assumptions. One such design is the crossover study in which patients are treated sequentially with each of two treatments and the objective is to compare the two treatment responses. In situations in which the effect of the first treatment may continue through the administration of the second (carry-over effect) or in which the disease is not stable and may progress by the time the second treatment is administered, the use of the crossover design may produce misleading results.⁴² Furthermore, dropouts that occur prior to administration of the second treatment have more impact on the statistical power of the test than occurs in the standard design.

One type of self-controlled study that occurs in otitis media is one in which the two ears of the same patient receive different treatments.^{43,44} A crucial aspect of such studies is the extent to which the treatment in a given ear may be affected by treatment in the opposite ear. Such a dependence is biologically plausible, since the nasopharynx provides a route of transmission of both fluid and organisms.

The most common study design in otitis media with effusion appears to be longitudinal; it is a design in which individuals are followed over a predetermined time period. This is to be contrasted with a cross-sectional study in which comparisons are made at a fixed point in time and the time point may not be the same for different individuals. The major advantage of longitudinal studies is that

TABLE 4. SAMPLE SIZE ESTIMATES FOR VARIOUS END POINTS IN TRIALS OF ACUTE OTITIS MEDIA WITH EFFUSION

End Point	Sample Size (Total for Both Groups)
OME at 15 d	154
OME at 30 d	80
No. of acute episodes in 3 mo	70
Percentage/time with OME in 3 mo	76
No. of initial treatment failures (failure to respond to first antibiotic)	1,912
OME — otitis media with effusion. $\alpha = .05$, two-sided, 50% reduction, $\beta = .10$.	

they provide an indication of various selection factors that may occur and prevent evaluation at future time points. Their major disadvantage is cost and amount of time until study completion when compared to a cross-sectional study. A higher dropout rate and missing observations also may complicate the analysis of a longitudinal study.

If a variable is related to outcome and also unevenly distributed in the two groups being compared, it may be a confounding variable. Potential confounding variables in otitis media include age, duration of disease, sex, race, laterality of disease, previous history of ear disease, and season at entry. Whether a factor is related to a specific outcome may depend on the definition of the disease. Thus, a variable may be a confounder for otitis media with effusion but not for acute disease. In studies at the OMRC conducted for otitis media with effusion (no acute disease), age was not a factor in predicting the presence of fluid at the 2-week outcome (Table 3). However, in studies of acute disease the presence of fluid was related to age at entry.

Finally, sample size estimates are a crucial part of any design, and they depend on the type of design as well as the type of outcome variables. Table 4 demonstrates the different sample size estimates that may result from various end points in studies of otitis media. All estimates have used baseline parameters from our studies at the OMRC and assume an $\alpha = 0.05$ two-sided test and a probability of 0.90 of detecting a 50% reduction in the end point measurement. Prior to initiating the study, an investigator needs to demonstrate that there is sufficient sample size to detect clinically important differences for the primary outcome.

In summary, the general questions of study design in otitis media are similar to those that have been observed in other areas of research. There is a continuing need for systematic analysis of large, well-controlled studies that will enable us to answer questions that are necessary in planning better-designed studies that can further enhance our understanding of the epidemiology and the treatment of otitis media.

INCIDENCE, PREVALENCE, AND NATURAL HISTORY OF OTITIS MEDIA IN DIFFERENT GEOGRAPHIC AREAS AND POPULATIONS

EPIDEMIOLOGY OF OTITIS MEDIA WITH EFFUSION IN JAPAN

TOMONORI TAKASAKA, MD

Otitis media with effusion is one of the most frequently occurring pediatric diseases in Japan, but its pathogenesis and possible risks are not thoroughly understood. The purpose of this study is to ascertain the prevalence of otitis media with effusion in Japan in children between the ages of 4 and 8 years, and to explore the predisposing factors for this disease through a carefully designed case-control study.

MATERIALS AND METHODS

Single Tympanometric Screening and Otolaryngologic Examinations. The subjects were 179 preschool children and 7,040 schoolchildren 6 to 8 years old living in Sendai city and its county. The tympanometric screenings were performed with a Teledyne Impedance Meter (TA-5A) in February 1986, and were evaluated by school otolaryngologists. None of the children complained of earache or of hearing difficulties on the day of the examinations. Parents of children with abnormal (type B or C2) tympanograms were advised to have further otolaryngologic examinations by specialists. We were informed of the final results by mail.

Age and Sex Distributions of Patients With Otitis Media With Effusion. These studies were performed at the Oita University Hospital and the Sendai Red Cross Hospital, respectively. The purpose of the study was to learn whether there were different distributions between the two hospitals at different geographic sites in Japan. Two hundred forty-four patients were seen at Oita from 1981 to 1986, and 360 patients were seen at Sendai from 1982 to 1986.

Case-Control Study. The subjects were 201 children 4 and 5 years of age; 67 of these had otitis media with effusion. The remaining 134 children were a control group matched to cases of otitis media with effusion by age, sex, and kindergarten class. Two control children per case were selected from the kindergartens in Sendai city and its county. Two well-trained interviewers visited the children's homes, interviewed the parents, and asked approximately 32 questions regarding infant care, irritant exposure, episodes of inflammatory or atopic diseases, etc. Data analysis was performed by the matched-pair method with use of a logistic regression model.

RESULTS

Tympanometric Screening. The prevalence of type B and C2 tympanograms from 14,509 ears examined was 8.7% in the target group of children. The highest prevalence was seen in 4-year-old children (19.3%), and it decreased with age as follows: 5-year-olds, 8.0%; 6-year-olds, 6.9%; and 8-year-olds, 3.6%. The boys with type B or C2 tympanograms were about 1.6 times more numerous than the girls. Four-year-old boys revealed a 29.5% prevalence of abnormal tympanograms, whereas only 3.0% was noted in 8-year-old girls. In 6- to 8-year-old children, 577 of 7,040 (8.5%) were advised to receive further specific otolaryngologic examinations, and 434 children were seen at the specialists' offices within a month after the ini-

tial school examinations. Two hundred twenty-two children of 434 (51.2%) were diagnosed as having otitis media with effusion. This indicates that the prevalence of this disease in healthy Japanese children between 6 and 8 years of age is about 3.0%. The highest prevalence was found in 6-year-old children (4.7%); it also decreased with age as seen in the prevalence of abnormal tympanograms.

Age and Sex Distributions of Patients With Otitis Media With Effusion. Of 360 patients with the disease, 245 patients (68.1%) were children between birth and 9 years of age in the Sendai Red Cross Hospital. This figure is comparable to that of 244 patients (70.5%) at the Oita University Hospital. The male to female ratio in children with otitis media with effusion was about 3:2 in both hospitals, but it was not obvious in the case of adults. The peak of the disease during childhood was found in 6-year-old children, and nearly 70% of those with otitis media with effusion were included within the range between 4 and 7 years of age. It was concluded that there were no marked differences in age and sex distributions between the two hospitals.

Risk Factors for Otitis Media With Effusion. Two hundred one children were identified as being similar in all socioeconomic and demographic categories. There were no significant differences in birth weight, early feeding pattern, and exposure to two or more household cigarette smokers. The risk for otitis media with effusion increased fivefold in children with episodes of acute suppurative otitis media, and this was confirmed to be statistically significant ($p < .01$). Atopy did not increase the risk, but nasal allergy showed nearly a twofold increase. Upper airway troubles such as snoring at night and hypertrophied tonsils increased the risk for otitis media with effusion. Other factors such as family history of atopy and middle ear disease did not increase the risk.

DISCUSSION

From our epidemiologic survey, we can conclude that the prevalence of otitis media with effusion in our group of healthy children between 4 and 8 years of age was comparable to that of a group in Finland.⁴⁵ Significant improvements with increasing age were observed in the prevalences of both abnormal tympanograms and otitis media with effusion, although young children between birth and 3 years of age were not included in this study. Similar results had been indicated previously by reports from Scandinavia,^{46,47} and it was suggested that the functions of the eustachian tube and the local defense system against microorganisms could be progressively improved with advancing age. This improvement will be accomplished around 8 years of age, so that additional episodes of otitis media with effusion during childhood are scarcely observed. As far as the age and sex distributions of the patients with the disease are concerned, there were no significant differences between the two hospitals. The peak of the age distribution was found at the 6-year-old group, and younger children 4 and 5 years of age were fewer in

number when compared to 6- and 7-year-old children. This indicates that younger children with otitis media with effusion in Japan are still rather unnoticed until they can express themselves. Therefore, it should be emphasized that repeat tympanometric screenings must be essential as a routine examination for detecting this childhood disease. A significantly high risk for otitis media with effusion is found in the number of episodes of acute otitis media in our case-control study. Although similar evidence is

also available from various countries,⁴⁸⁻⁵⁰ our study must be the most severely analyzed case-control study, since we used a very strict matched-pair method. Consequently, we strongly suggest that microorganic invasions of the middle ear cleft play an important role in initiating otitis media with effusion during childhood, and our efforts should be directed toward reducing the incidence of acute otitis media in young children. Polysaccharide vaccination could be one of the most powerful candidates for this purpose.

POINT PREVALENCE OF SECRETORY OTITIS AT DIFFERENT AGES

MIRKO TOS, MD; SVEN-ERIC STANGERUP, MD; GERD HVID, MD; ULRİK KOKS ANDREASSEN, MD

INTRODUCTION

Since 1977, three cohorts of otherwise healthy children have been tested with tympanometry at a total of 36 screening trials. The first cohort was followed from birth to the age of 8 years,⁵¹ the second from the age of 2 to 9 years,⁵² and the third from the age of 4 to 10 years.⁵³⁻⁵⁶ These investigations have provided us with a wealth of epidemiologic information about secretory otitis, including the point prevalence, period prevalence, incidence, and natural history of the disease. In this study our data on the point prevalence of secretory otitis are summarized and discussed in relation to the age of the children.

MATERIAL AND METHODS

The size of the series, the age of the children at the individual screening trials, and the time of the trials are indicated in Table 5. Details concerning the origin and composition of the cohorts have been described previously.^{51,56} Cohort I comprised 150 children consecutively born in the maternity ward of the Gentofte Hospital from January through April 1977.⁵¹ Cohort II comprised 278 healthy children from a geographically well-defined area of two municipalities in Copenhagen County comprising 120,000 inhabitants⁵²; the children were born during the first 10 days of every month in 1976. Cohort III⁵³ comprised 373 healthy children born during the first 10 days of every month in 1978 and living in two other municipalities in Copenhagen County that total 130,000 inhabitants. Tympanometry was performed with a Madsen ZO70 impedance meter at a frequency of 220 Hz. Each examination included otoscopy and otomicroscopy.⁵⁴⁻⁵⁶

POINT PREVALENCE RATE

The point prevalence rate of type B tympanometry indicates the percentage of ears with type B tympanograms at a certain point in time. Middle ear effusion has been demonstrated by several authors in 80% to 100% of children with type B tympanograms and in 15% to 50% of ears with type C2. The prevalence of type B determined at the individual tympanometric screenings thus may be taken to indicate the prevalence of secretory otitis with middle ear effusion.

At birth, none of the ears had a type B or type C2 tympanogram. Only one ear had a middle ear pressure of -125 mm H₂O, and the remaining ears had normal middle ear pressures (0 to -99 mm H₂O) (Table 5). During the first 3 months and even more pronouncedly during the ensuing 3 months, the tympanometric conditions gradually deteriorated. At 6 months 10% of the ears had type C2

and 1% had type B. From 6 to 12 months there was a further deterioration, and at 1 year 13% of the ears had type B and 19% had type C2 tympanograms. Such a high prevalence of secretory otitis during infancy was a big surprise for us in 1978, particularly because the majority of children had no symptoms of ear disease and relatively few infants received surgical treatment for secretory otitis. Furthermore, this finding makes it probable that quite a number of the children admitted for surgical treatment of secretory otitis at 3 to 4 years of age have had the disease since infancy.

At age 2, the prevalence of secretory otitis ranged from 10% to 14% in cohorts I and II (Table 5). During winter, however, cohort I showed a prevalence of 18%, which is the highest rate of secretory otitis we have observed in any of our cohorts. In August 1978, when the summer in Denmark was exceptionally warm and sunny, the prevalence reached only 7%, which is the lowest rate we have ever demonstrated among young children. Concordantly, the prevalence of type A was 64% at the same trial (Table 5). At age 3, the point prevalence of type B was almost the same as in the 2-year-old children, that is, 9% in cohort I and 11% in cohort II (Table 5). At age 4, cohort III was more thoroughly investigated, with tympanometry being performed every third month; the point prevalence of type B ranged from 10% to 14%. A similar prevalence was found for cohort II, whereas cohort I showed a prevalence of 17%.

At age 5, the point prevalence was still as high as 18% in cohort III (Table 5), whereas in cohorts I and II it was 13% and 11%, respectively. At age 6, age-related spontaneous improvement could be demonstrated in cohort I, where the prevalence of type B was now 3%, whereas in cohorts II and III it was 9% and 14%, respectively (Table 5). At age 7, there was a considerable improvement of the tympanometric conditions and a decrease in the point prevalence of secretory otitis in all three cohorts, although the point prevalence rate of type B was still 7% in cohorts II and III (Table 5). At ages 8 and 9, the point prevalence rate was low in all three cohorts, ranging from 2% to 4%, and the percentage of ears with type A tympanograms increased correspondingly; these findings confirm that spontaneous improvement of the tubal function can be related to the age of the child. At age 10, the point prevalence of type B was 2% in cohort III (Table 5).

Annual screening trials are being continued in these three cohorts, and in February 1986, when the children were 9, 10, and 11 years of age, respectively, the preva-

TABLE 5. POINT PREVALENCE OF SECRETORY OTITIS AND DISTRIBUTION OF TYMPANOGRAM TYPES IN THREE DIFFERENT COHORTS OF RANDOMIZED OTHERWISE HEALTHY CHILDREN

Cohort	Screening No.	Age	Time of Tympanometry (mo/yr)	No. of Ears	Tympanogram Types				χ^2 Test
					A	C1	C2	B	
I	1	2-4 d	1-2/77	300	90	10			p < .001
	2	3 mo	5/77	252	82	17	1		p < .001
	3	6 mo	8/77	238	62	27	10	1	p < .001
	4	9 mo	11/77	236	47	38	11	4	p < .001
	5	12 mo	2/78	206	40	28	19	13	p < .001
	6	15 mo	5/78	132	43	24	19	14	p < .001
	7	18 mo	8/78	132	45	28	15	12	
	8	21 mo	11/78	132	42	20	19	19	
	9	24 mo	2/79	132	39	26	21	14	p < .001
	10	3 yr	2/80	170	26	28	38	9	p < .001
	11	4 yr	2/81	144	20	35	27	17	p < .001
	12	5 yr	2/82	124	40	28	19	13	p < .001
	13	6 yr	2/83	106	37	26	34	3	p < .001
	14	7 yr	2/84	154	61	27	8	4	p < .001
	15	8 yr	2/85	148	65	28	10	3	
II	1	2 yr	11/77	556	50	19	20	11	
	2	2 yr	2/78	508	47	18	20	14	p < .001
	3	2 yr	5/78	480	52	22	15	11	p < .001
	4	2 yr	8/78	440	64	19	11	7	p < .001
	5	3 yr	2/79	404	47	24	18	11	p < .001
	6	4 yr	2/80	368	37	22	27	14	p < .01
	7	5 yr	2/81	280	37	22	29	11	p < .01
	8	6 yr	2/82	254	43	24	24	9	p < .01
	9	7 yr	2/83	230	51	26	17	7	p < .01
	10	8 yr	2/84	250	78	16	4	2	p < .01
	11	9 yr	2/85	262	63	27	8	2	
III	1	4 yr	2/79	746	36	21	29	14	p < .001
	2	4 yr	5/79	670	41	25	23	11	p < .001
	3	4 yr	8/79	666	38	29	23	10	p < .001
	4	4 yr	11/79	576	32	31	23	14	p < .001
	5	5 yr	2/80	628	27	25	31	18	p < .001
	6	6 yr	2/81	538	30	27	28	14	p < .001
	7	7 yr	2/82	590	43	23	27	7	p < .001
	8	8 yr	2/83	412	50	28	18	4	p < .001
	9	9 yr	2/84	406	61	22	15	3	p < .001
	10	10 yr	2/85	470	67	19	12	2	p < .001

Tympanogram type A indicates middle ear pressure of 0 to -99 mm H₂O; type C1, -100 to -199 mm H₂O; type C2, -200 to -350 mm H₂O; and type B, flat curve without impedance minimum.

Probabilities refer to time (age) within same cohort. Statistic could be made between all ages between different cohorts, eg, screening between 1 and 4 and between 4 and 6. Blank space indicates that there was no testing between particular ages, eg, screening between 7 and 8 and between 14 and 15.

lence of secretory otitis was as low as in the preceding years.

The number of children in the three cohorts is diminishing gradually, either because the children no longer wish to participate or because they have moved to other parts of the country. Over the years we have undertaken numerous statistical tests showing that the tympanometric conditions in the deserting children at the preceding trial did not deviate significantly from those found in the attending children. Thus, the reduced series can still be regarded as representative for the original cohorts.⁵¹⁻⁵⁶

Seasonal Variations in Point Prevalence. The point prevalences of secretory otitis and tubal dysfunction have been known to differ significantly with the season of the year. Thus, the tympanometric conditions in cohort II improved markedly from February to May and from May to August 1978 (Table 5), whereas a significant deterioration from summer to winter took place from August 1978 through February 1979.⁵⁴

Similarly, in cohort III, a significant improvement was demonstrated from February 1979 to May 1979 as the conditions deteriorated, and the point prevalence of secretory otitis increased from summer to winter (Table 5).

In general, the tympanometric conditions were better in cohort II than in cohort I at the ages of 2 and 4 years (Table 5). Similarly, the conditions were generally better in cohort II than in cohort III at the ages of 4 and 5 years. This applied also to the frequency and degree of severity of sequelae changes of the eardrum, which were most pronounced in cohort III. Perhaps the pronounced improvement from winter to summer in 1978 when the children in cohort II were 2 years of age had a favorable influence on the conditions also during the ensuing years. The children in cohort III were 3 years of age in 1978, and it is conceivable that the winter-summer improvement was not so marked in this age group.

Since the children in cohort II were selected so that all children born during the first 10 days of every month in

TABLE 6. IMPROVEMENT TO BETTER TYPE OR DETERIORATION TO WORSE TYPE AMONG DIFFERENT EVALUATIONS OF THREE SERIES

Cohort	Period of Evaluation (mo/yr)	Length of Period	Percentages of All Types			Percentage of Type B Improved
			Improved	Deteriorated	Unchanged	
I	2-5/77	3 mo	1	23	76	—
	5-8/77	3 mo	12	32	56	—
	8-11/77	3 mo	17	33	51	25
	11/77-2/78	3 mo	17	35	48	18
	2-5/78	3 mo	23	30	47	27
	5-8/78	3 mo	23	19	58	38
	8-11/78	3 mo	17	33	50	19
	11/78-2/79	3 mo	21	23	56	44
	2/79-2/80	1 yr	19	34	47	58
	2/80-2/81	1 yr	27	27	46	47
	2/81-2/82	1 yr	53	19	28	78
	2/82-2/83	1 yr	34	35	31	90
	2/83-2/84	1 yr	40	10	49	67
	2/84-2/85	1 yr	22	18	59	50
II	11/77-2/78	3 mo	26	26	48	50
	2/78-5/78	3 mo	30	18	52	63
	5/78-8/78	3 mo	30	18	52	76
	8/78-2/79	6 mo	16	35	50	48
	2/79-2/80	1 yr	20	36	44	58
	2/80-2/81	1 yr	24	26	50	59
	2/81-2/82	1 yr	35	24	40	58
	2/82-2/83	1 yr	32	21	47	63
	2/83-2/84	1 yr	49	6	46	100
	2/84-2/85	1 yr	12	33	55	40
III	2/79-5/79	3 mo	32	21	47	59
	5/79-8/79	3 mo	25	27	48	39
	8/79-11/79	3 mo	20	32	49	27
	11/79-2/80	3 mo	23	36	41	46
	2/80-2/81	1 yr	42	22	36	55
	2/81-2/82	1 yr	46	17	38	84
	2/82-2/83	1 yr	35	22	43	75
	2/83-2/84	1 yr	32	22	46	77
	2/84-2/85	1 yr	26	19	55	67

1976 were included, they represent one third of all children born that year. At the individual trials, however, they were not exactly of the same age. Thus, at the first trial in November 1978, the age of the "2-year-old" children varied in age from 1 to 2 years, and the "4-year-old" children varied in age from 3 to 4 years. The children in cohort I are more homogeneous in that the age difference between the youngest and the oldest child is only 3 months. These age differences among children in the same cohort and among the individual cohorts perhaps may explain the differences in the point prevalence among the cohorts at the same age.

DYNAMICS OF TUBAL DYSFUNCTION

The point prevalence rates of secretory otitis mentioned here can be regarded as "snapshots" illustrating the great variability of the tympanometric conditions, which our repetitive screenings performed every third month also make evident (Table 6).⁵¹⁻⁵⁶ In all three cohorts almost half the ears changed type between each trial: some deteriorated, and others improved. In cohort I the deteriorations were predominant during the first year of life, and this clearly could be correlated to upper respiratory tract

infections.⁵¹ At the age of 2 to 5 years, deteriorations and improvements were almost equally frequent, but after the age of 5 years the improvements predominated. It is far from the same ears that change type between each trial, which further adds to the complexity of the matter.

Spontaneous recovery of type B tympanograms, which at each trial could be demonstrated in almost half of the ears (Table 6), likewise illustrates the described dynamics of the tympanometric conditions that result from improvements or cessation of the different etiologic factors influencing the mucosa of the eustachian tube and the middle ear — most often upper respiratory tract infections.

The demonstration of such high rates of spontaneous improvement of secretory otitis, which may be seen in all age groups (Table 6), is perhaps the most important result of our repetitive screenings and a result that must be taken into account when considering the indications for surgical treatment of secretory otitis. Likewise, it emphasizes the need for critical evaluation of the results of medical treatment of secretory otitis, since obviously spontaneous improvement represents the placebo effect.

OCCURRENCE OF ACUTE OTITIS MEDIA IN CHILDREN: COHORT STUDIES IN AN URBAN POPULATION

LEIF INGVARSSON, MD; KAJ LUNDGREN, MD; CECILIA STENSTROM, MD

INTRODUCTION

Acute otitis media is the most common bacterial complication of upper respiratory tract infections in childhood. Children with single episodes of acute otitis media are in most cases easy to treat. Children with repeated episodes of acute otitis media offer special problems of a medical and socioeconomic character, and there are so far no signs that the quantitative importance of the middle ear diseases is diminishing.

The interest in epidemiologic studies of acute otitis media in children has increased during later years among otolaryngologists and pediatricians.⁵⁷⁻⁶¹ It has been pointed out that prospective longitudinal studies covering representative populations in different parts of the world and followed up for a number of years are needed. One of the most important long-range goals will be to identify as early as possible the otitis-prone children and to find different factors contributing to this condition, with the intention of preventing these factors.

The city of Malmö, Sweden, offers unique conditions for epidemiologic studies, with a well-defined population in a restricted geographic area. These circumstances have been used in earlier epidemiologic studies of different diseases and were a contributory cause in starting a prospective cohort study of the incidence of acute otitis media in children at the otolaryngology department at Malmö General Hospital in 1977.

The aim of this paper is to summarize the results from the study presented and published earlier⁶²⁻⁶⁶ concerning the incidence of acute otitis media among children in relation to age, sex, season, and different socioeconomic factors, and to give some preliminary results from a separate study of children with recurrent episodes of acute otitis media early in life.

MATERIALS AND METHODS

The prospective cohort study of the incidence of acute otitis media in children started in 1977 and was completed in 1986, ie, 10 years in total. All doctors working at the otolaryngology and pediatric departments at Malmö General Hospital, as well as all individual general and private practitioners in the city, took part in the study. All children born in Malmö in 1977 or later and diagnosed for acute otitis media were registered. The registration included the patient's name, 10-digit birth number, and date and place of diagnosis. Information about the patient's dwelling in the city, type of housing, and type of day-care at time of diagnosis was collected from different official computerized sources. All information was computerized and processed in a specially designed statistical program.

The following presentation includes results from the first 7 years of the registration, 1977 to 1983. Different birth cohorts were followed up for 4 to 7 years with regard to different epidemiologic aspects.

A group of 252 children born in 1977 to 1981, identified from the incidence study, and registered for six or more episodes of acute otitis media before the age of 2 years

(otitis-prone children) was followed separately. The otitis-prone group consisted of 154 boys (61%) and 98 girls (39%). A control group including the same number of children with the same age and sex distribution was chosen by chance from the population. The medical records from the otolaryngology and pediatric departments for all the 504 children were studied with regard to ambulatory visits, hospital admittances, different otolaryngologic operations, and other diagnosed diseases.

RESULTS

During the years 1977 to 1983, 16,611 children were born in Malmö. At the end of 1983, 6,893 (79%) of the boys and 6,127 (77%) of the girls had been registered for 13,990 and 11,921 episodes of acute otitis media, respectively. The annual incidence rate was highest in 1-year-old children. In this age group 35% of the boys and 30% of the girls had at least one episode of acute otitis media. The attack rate, ie, the number of episodes per 100 children at risk, was also highest in 1-year-old children for both boys and girls.

The cumulative incidence rate of the first episode of acute otitis media in children born from 1977 to 1983 in relation to sex is shown in Fig 2. At the age of 3 years, 50% of all the boys had had at least one episode of acute otitis media, while 50% of the girls had experienced their first episode 7 months later. At the age of 7 years, about 65% to 70% of all the children had suffered at least one episode of acute otitis media. The greatest risk of getting the first episode of acute otitis media was seen between 6 and 11 months of age for both boys and girls.

The seasonal variation of the incidence of acute otitis media is very consistent from one year to another, and only small differences are seen between the years. The greatest number of episodes was noted during winter, with a peak in December. The smallest figures were seen during the summer months of June to August.

The cumulative incidence rate of acute otitis media

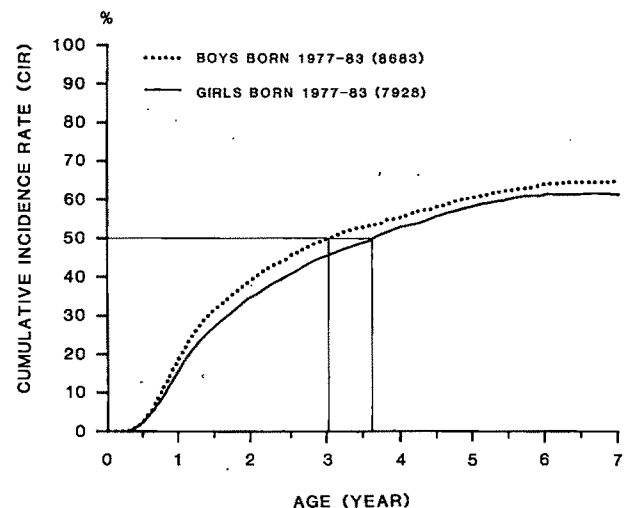


Fig 2. Cumulative incidence rate of first episode of acute otitis media in relation to sex.

TABLE 7. AGE AT FIRST EPISODE OF AOM IN RELATION TO NUMBER OF EPISODES OF AOM PER CHILD

No. of Episodes per Child	Age at First Episode							
	<1 yr		1 yr		>2 yr		Total	
	No.	%	No.	%	No.	%	No.	%
1	295	28	407	41	650	69.0	1,352	45
2-3	430	41	411	42	257	27.5	1,098	37
4-5	200	19	128	13	30	3.0	358	12
6-16	130	12	35	4	5	0.5	170	6
Total	1,055	100	981	100	942	100.0	2,978	100
AOM — acute otitis media.								

AOM — acute otitis media.

among children born in 1977 and living in different districts and different types of houses in the city of Malmö was studied in three different districts (center of the city, Rosengård, and Oxie). In the center of the city most families live in older, mainly well-maintained apartment houses. Rosengård is a modern crowded tenement house district built in the 1960s and 1970s. Oxie is a modern crowded villa suburb outside Malmö built in the later 1970s. The children living in Oxie had the highest cumulative incidence rate. At the end of the observation period of 5 years, about 65% of the children had had at least one episode of acute otitis media with effusion. The corresponding figures for the children living in Rosengård and in the center of the city were about 55% and 45%, respectively. The differences among the districts were significant ($p < .001$).

In order to study the importance of day-care type and the importance of age at first episode to the total number of episodes per child, 2,978 children were followed during their first 4 years of life. The children were born from 1977 to 1979 and had been registered for at least one episode of acute otitis media. Among children attending public day-care centers for the first time before the age of 2 years, 8% were registered for six or more episodes of acute otitis media during their first 4 years of life. In children attending public day-care centers for the first time between the ages of 2 and 3 years, 5% had six or more episodes of acute otitis media during the corresponding time. For children cared for at home or privately during their first 4 years of life, 3% were registered for six or more episodes of acute otitis media. The difference between the groups was statistically significant ($p < .001$).

Table 7 shows the age at the first episode of acute otitis media in relation to the total number of episodes per child during the first 4 years of life. Forty-five percent of the children had only one episode, while 6% were registered for six or more episodes. Among 1,055 children having their first episode of acute otitis media before the age of 1 year, 12% were registered for six or more episodes. The

corresponding figure among 942 children having their first episode after the age of 2 years was 0.5%. The difference between the groups was significant ($p < .001$).

The study of the medical records of 504 children from the otolaryngology and pediatric departments showed that the otitis-prone children were registered for a mean number of 39 ambulatory visits per child during their first 4 years of life, as compared to 9 visits per child in the control group.

In the otitis-prone group myringotomy was performed at least once in 67% of the children. Fifty-two percent had tympanostomy tubes inserted and 19% had undergone adenoidectomy. The corresponding figures from the control group were myringotomy, 13%; tympanostomy tubes, 6%; and adenoidectomy, 6%.

The occurrence of other diseases diagnosed in the children showed that in the otitis-prone group, 53% had been found to have bronchopulmonary diseases at least once, 44% had been treated for gastrointestinal diseases, and 36% had been found to have allergic symptoms or diseases at least once. The corresponding figures for the control group were bronchopulmonary diseases, 32%; gastrointestinal diseases, 33%; and allergic symptoms or diseases, 17%. The difference between the two groups was statistically significant ($p < .001$).

CONCLUSIONS

The incidence rate of acute otitis media was highest in 1-year-old boys. At the age of 3 years, about 50% of all children in Malmö had had at least one diagnosed episode of acute otitis media. At the age of 7 years, the corresponding figures were 65% to 70%.

The incidence of acute otitis media was found to vary among children living in different districts and in different types of housing in the city. Children attending public day-care centers early in life were more prone to recurrent episodes of acute otitis media than those attending public day-care at later ages, or those children cared for at home or in private care.

Children having their first episode of acute otitis media before the age of 1 year run a greater risk of being otitis-prone than those having their first episode after the age of 1 year. Children with recurrent episodes of acute otitis media early in life also seem to be more prone than other children to other kinds of diseases, ie, bronchopulmonary, gastrointestinal, and allergic diseases.

It is important to detect and recognize otitis-prone children as early as possible in order to be able to offer them treatment and long-range control.

ESTIMATING THE RISK OF ACUTE OTITIS MEDIA AMONG URBAN CHILDREN

JUHANI PUKANDER, MD; MARKKU SIPILÄ, MD; MATTI KATAJA, PhD; PEKKA KARMA, MD

Acute otitis media is an increasingly important health problem among the pediatric population. Only a few children escape acute otitis media during their childhood days.⁶⁷ Many factors may affect the liability of a small child to contract acute otitis media. These factors are un-

dergoing continuous change along with changes in the way of living and behavior of the entire society. One of the most prevalent changes is the arrangement of day-care for children, because increasingly both parents are working outside the home.⁶⁸

TABLE 8. STEPWISE MULTIVARIANT ANALYSIS OF INTERRELATED POWER FUNCTION OF VARIABLES AFFECTING OCCURRENCE OF AOM AMONG 1,294 CHILDREN

	Rank of Importance Along With Minimum No. of AOM Attacks per Child					Correlation Coefficient (r) of Separate Variables Affecting Occurrence	
	1	2	3	4	5	Children With at Least 1 AOM Attack (no/yes)	Total No. of AOM Attacks per Child
Attending day-care center	1	1	1	1	1	0.161*	0.263*
Sibling(s) with AOM attacks during follow-up	4	2	2	2	2	0.129*	0.142*
Attending family day-care	8	4	5	3	9	0.068†	-0.009
Type of housing	3	6	9	9	7		
Smoking of parent(s)		8	6	4	4		
Mother's respiratory infections before follow-up	5	3	11	11		0.062	0.023
Birth weight	15	11	3	10	10	0.032	0.009
Father's respiratory infections before follow-up	11	7	8			0.009	-0.003
Nighttime bottle in supine position			10	6	6	-0.026	-0.001
Floor area per person at home			13	5	3	-0.008	-0.056
Viral respiratory infections and tonsillitis of sibling(s) during follow-up	2	9			5	0.123*	0.079†
Socioeconomic status	7		7			-0.030	-0.050
Pets	13			8		-0.093§	-0.023
Allergy of parent(s)	14			12		-0.015	0.004
Breast-feeding		13	4			0.024	-0.015
Indoor humidification	9	10	12			0.088§	0.087§
Sex (boys had more AOM attacks)	10	12				0.015	0.076†
Allergy of child	12	5				0.081†	0.062
Respiratory infections of parent(s) during follow-up	6				8	0.093§	0.053
Place of residence				7			
No. of siblings						0.065†	0.090§
Positive otitis history of parent(s)						0.101§	0.097§

AOM — acute otitis media.

*p < .001.

†p < .05.

§p < .01.

In addition to human suffering, recurrent otitis attacks with effusion inside the middle ear impair the child's hearing ability at an age that is critical for the acquisition of linguistic skills. Children who have had prolonged middle ear effusion have shown depressed scores on intelligence tests, impaired development of speech and language, and poor performance in school.⁶⁸ The preventive procedures for this common and harmful illness are by no means composed only of medical aspects. Social and health educational factors play a very important role, too. That is why we are trying to analyze the combined risk of acute otitis media with a multivariate forecasting model.

The present analysis comprised a cohort of 1,294 children followed from the age of 7 months to the age of 2 years. Relevant epidemiologic data were collected during their regular checkup visits at child health-care centers, and their ears were examined and disorders were treated in specific study clinics.

A forecasting model for calculating the interrelative importance of given risk indicators was developed.⁶⁹ This mathematic method, ie, to find the best forecasting model in the Bayesian sense, follows the idea of stepwise multiple regression analysis, searches through all variables listed, and selects one by one the variable improving the model most, or at least affecting it with the fewest drawbacks if not improving it. The worth of the model is measured by

the sum of false negatives and false positives. The minimum of this sum builds the optimum of the model. The variables in this list above this optimum affect the risk, with the rest of the variables being no longer useful in this forecasting model. In other words, the Bayesian approach reveals the variables containing any noticeable influence on the occurrence of acute otitis media. In our hands this model gave a correct classification in 65% to 71% of the cases; the higher the percentage, the higher the number of recurrent attacks per child.

Of the 22 variables studied, 12 to 15 were found to affect the combined risk of contracting one or more attacks of acute otitis media. The rank of importance of these 22 variables is shown in Table 8, indicating the interrelated power function of different variables in contracting acute otitis media.

The overwhelmingly highest risk indicator was day-care outside the study child's own home, regardless of how many recurrent attacks of acute otitis media were included in the analyses. However, this risk indicator became more important along with the increased number of recurrent attacks. Acute otitis media currently is preceded very often by upper respiratory tract infections,⁷⁰ and such infections tend to spread more easily the higher the population density. Day-care nurseries create a favorable environment for respiratory viruses to spread,⁷¹ with acute

otitis media as a sequela. Next in the risk indicator list came the number of attacks of acute otitis media among siblings, most probably because of increased exposure of a baby to infections brought in from outside the home; this was especially true with recurrent attacks. The same phenomenon can be seen with the type of housing, also.⁷² The bigger the house with very many families living there, ie, apartment buildings, the higher the concentration of virus particles in the air inhaled by a baby.

Passive smoking is quite newly observed as a risk factor for acute otitis media, although there are contradictory reports on this point.⁷¹⁻⁷³ Our results showed that the mother's smoking seemed to increase most the risk to the baby of contracting acute otitis media and especially of contracting recurrent attacks. The number of smoking mothers in Finland is fortunately low, but on the other

hand, because of this, information is sparse, and very definitive conclusions could not be drawn in this study. The protective effect of prolonged breast-feeding against respiratory infections is well known,⁷⁴ whereas data on its protective effect against acute otitis media are, however, now accumulating.⁷⁵ Our patients seemed to enjoy some protection against acute otitis media, but only during the first 12 months of life, ie, during breast-feeding time. Breast-feeding babies is becoming more fashionable again after a period of underrating this natural way of nourishment,⁷⁶ so future studies will reveal the optimal length of this "therapy."

In conclusion, this study suggests that the best place for a small child during the first years of life is in his own house where the mother breast-feeds him and does not smoke.

CURRENT STATUS OF OTITIS MEDIA IN THE AMERICAN INDIAN POPULATION

JOSEPH L. STEWART, PHD

The opinions expressed in this paper are those of the author and do not necessarily reflect the views of the Indian Health Service, US Public Health Service.

Incidence and prevalence determinations for a given disease typically involve specific research designs for those purposes. In the Indian Health Service (IHS), where resources for research are lacking, it is usually necessary to make prevalence estimates inferentially from assessing hospital records. The data in this report are based upon the number of visits for acute and chronic otitis media, with individual patients unspecified, and analyses of actual patient counts.

Otitis media was first listed in the IHS as a reportable disease in 1962. It has been no lower than the second highest in annually reported visits since that time, even though a special program was begun in 1970 to provide for the remediation and control of otitis media in American Indian and Alaska Native communities throughout the United States.

Over the 15 years of the otitis media program's existence (Table 9), hospital visits for acute and chronic otitis media have increased by 44%. During the same time the patient population has increased by 49%. The ratio of first visits to revisits changed over the first 10 years. For acute otitis media, the first visit to revisit ratio has changed from 62% to 54% for the first visit only. For chronic otitis media, the ratio has been more constant, from 32% to 38% for the first visit only. These data indicate increased awareness for follow-up for acute otitis media and less concern for follow-up for chronic otitis media. These findings, and all others not otherwise referenced, are from internal reports compiled by the IHS (Table 9).

An observation of particular interest in Table 9 is the consistency in the number of diagnoses of acute versus chronic otitis media in spite of the absence of IHS-wide criteria for defining acute and chronic disease. In general, the diagnosis of the physician is tabulated as recorded. In his assessment of patient care records, Toubbeh⁷⁷ found that in Alaska, Montana, and southern Arizona there was a high consistency in the diagnoses of chronic disease based upon presence of perforation, duration of the episode, and

time between episodes. In Alaska, where 26.9% of the diagnoses were termed chronic otitis media, 1.1% showed perforation; in Montana, 9.5% cases were diagnosed chronic, with 0.8% showing perforation; in southern Arizona, 10.1% were diagnosed chronic, with 0.4% showing perforation. The consistency in diagnoses over time in Table 9 is noteworthy considering the IHS physician turnover rate and the wide variety of medical backgrounds of those making the diagnoses.

Evaluation of hospital records over the years of the program's existence shows three variables — sex, age, and blood quantum — to be particularly significant in making inferences about the natural history of otitis media.

TABLE 9. NUMBER OF OUTPATIENT VISITS FOR ACUTE AND CHRONIC OTITIS MEDIA, FISCAL YEARS 1971 TO 1985

Fiscal Year	Acute Otitis Media		Chronic Otitis Media		Total
	No. of Visits	%	No. of Visits	%	
1985	135,941	72.7	51,126	27.3	187,067
1984	129,022	71.7	50,731	28.3	179,753
1983	120,330	70.7	49,851	29.3	170,181
1982	108,561	69.8	47,029	30.2	155,590
1981	97,415	65.6	51,121	34.4	148,536
1980	90,408	70.0	38,668	30.0	129,076
1979	87,965	71.2	35,539	28.8	123,504
1978	95,692	81.5	21,671	18.5	117,363
1977	83,787	80.2	20,651	19.8	104,438
1976	81,126	79.5	20,941	20.5	102,067
1975	76,889	77.5	22,364	22.5	99,253
1974	74,915	78.3	20,717	21.7	95,632
1973	80,508	79.0	21,382	21.0	101,890
1972	74,107	77.7	21,312	23.3	95,419
1971	60,486	73.6	21,723	26.4	82,209

From Program Statistics Branch, Indian Health Service, Public Health Service, Department of Health and Human Services, Rockville, Md.

TABLE 10. NUMBER OF OUTPATIENT VISITS FOR ACUTE AND CHRONIC OTITIS MEDIA FOR INFANTS 1 YEAR OF AGE OR UNDER FOR FISCAL YEARS 1981 TO 1985

	%	No.	Total
Fiscal year 1981			
AOM	74	29,624	12.3
COM	26	10,529	4.4
Total		40,153	16.7
Fiscal year 1982			
AOM	75	32,932	13.2
COM	25	10,776	4.3
Total		43,708	17.5
Fiscal year 1983			
AOM	77	36,988	14.2
COM	23	11,330	4.4
Total		48,318	18.6
Fiscal year 1984			
AOM	76	38,946	15.2
COM	24	12,063	4.7
Total		51,009	19.9
Fiscal year 1985			
AOM	78	41,253	15.4
COM	22	11,761	4.4
Total		53,014	19.8

Outpatient visits include well-baby clinic, hospital/surgical follow-up, physical examinations, tests (laboratory, x-ray), socioeconomic, environmental problems, etc.

AOM — acute otitis media, COM — chronic otitis media.

AGE

Indian persons of all ages seek treatment for otitis media. While otitis media is primarily a disease affecting children, 1.4 % of the hospital visits for acute otitis media and 1 % of the visits for chronic otitis media on the Navajo reservation, for example, are made by persons 65 years of age and older. For all of the IHS, nearly 20 % of all hospital visits for children under the age of 1 year are for otitis media (Table 10), making it the most prevalent disease affecting children at this age. In children under the age of 15 years, otitis media was the leading reported disease in 1983 to 1985, being surpassed only by upper respiratory tract infections in 1981 and 1982. The overall percentage of visits for acute and chronic disease for persons of all ages has remained between 4.06 and 4.89 of total hospital visits in the years 1981 to 1985.

A 2-year (1980 and 1981) comparison of records from hospitals on the Navajo reservation, where otitis media is particularly prevalent, shows over 60 % of the total first patient visits have been made by children under the age of 5 years. The number of visits gradually declined by early adulthood, with a minor peaking again noted for both acute and chronic disease between 25 and 44 years of age, declining again through old age. While specific percentages vary among the tribes, this pattern is consistent over time throughout the reservations.

Recent analyses by Toubbeh⁷⁷ of over 17,000 individual patient records from three widely diverse areas showed a peak prevalence of otitis media at the age of 1 year in Alaska and Montana and 1½ years in southern Arizona. In common with the Navajo data, otitis media is seen throughout the life span in these areas.

Research on prevalence of otitis media during the first

year of life in two Alaskan Service Units indicates 1) high but markedly different rates and 2) the extent of other conditions during this critical year.⁷⁸ In Point Barrow, Alaska, 55 of 59 infants born in fiscal year 1984 had at least one episode of otitis media during the first year of life (93.2 %). In decreasing order of occurrence the data also show histories of bronchitis/bronchiolitis, pneumonia/pneumonitis, conjunctivitis, diarrhea, and relatively infrequent other problems. The infants with otitis average 2.7 other such conditions each, compared with eight conditions among the four children (2 %) with no history of otitis. At Bethel, Alaska, 212 of 285 infants born during the same time had at least one episode during the first year (74.4 %). Their records also reveal similar patterns of other diseases. Children with otitis averaged 2.3 other conditions; children with no otitis averaged 1.1.

SEX

On the Navajo reservation, sex distributions would indicate otitis media is more frequent among females, with 53 % of acute cases and 55 % of chronic cases consistently reported affecting females. As the male to female ratio on this reservation is 48 %:52 %, females predominate only slightly in visits for chronic disease. Other data in which the ratio of males to females is not accounted for indicate slightly more males than females affected. Sex and age on the Navajo reservation appear to be linked to severity, with boys being seen more often from birth through 4 years of age for both chronic and acute disease. This ratio is reversed for the most part through the remaining age ranges. Under the age of 1 year, the most critical so far at risk for repeated episodes and long-term sequelae are concerned, male to female patients consistently approximate the ratio of 52 % to 48 % for acute otitis media and 54 % to 46 % for chronic otitis media.

The most recent comparison of sex differences IHS-wide, from a recent Office of Technology Assessment report (1984 data),⁷⁹ reveals that otitis media accounted for 5.7 % of all outpatient encounters for males and 3.7 % of all encounters for females.

RACE AND GENETIC FACTORS

Marked racial differences within the general population of Indians and Alaskan natives have been demonstrated repeatedly, with two internal IHS reports of particular interest. L. Corkery, in 1973, reviewed 162 patient charts on a reservation in Wyoming and found the incidence for perforations to be 10 times higher for full-blooded Indians compared with those who were one-half Indian or less (unpublished report to Billings Area Office, IHS). Half-blooded Indians had a perforation rate seven times that of those with less than one-half blood quantum. Corkery pointed out that because of living conditions on the reservation it was impossible to factor out environmental from genetic elements.

B. S. Watrous et al in 1980 found marked differences in rates of otitis media in an institutionalized population in New Mexico in which all environmental conditions were identical (unpublished data, IHS). Otitis media was most severe in Navajo and Apache Indians, followed by Pueblo Indians and Hispanics, and was least severe for white people.

Further support for a genetic link, which supports Doyle's⁸⁰ otologic findings, can be determined from IHS

1980 data on percentages of patients' first visits for ear disease, with the highest average (8.0%) from Alaska, reflecting a large number of Eskimo patients, followed by the Navajo average (7.3%) — findings that are consistent with other available data.

No previously unpublished data are available from IHS sources on other variables such as climate, geography, environmental factors, breast-feeding versus bottle feeding, etc, that may be significant in studying the natural history of otitis media.

OTITIS MEDIA IN FOUR POPULATIONS OF ARIZONA INDIAN CHILDREN

NORMAN WENDELL TODD, JR, MD

This project was funded by the Indian Health Service and was conducted jointly with the Department of Family and Community Medicine, College of Medicine, University of Arizona, in cooperation with tribal health departments.

The opinions expressed in this paper are those of the author and do not necessarily reflect the views of the Indian Health Service, US Public Health Service.

BACKGROUND

Morbidity data in the 1960s indicated otitis media in Indian populations to be a continuing problem, at a prevalence of perhaps 15 times that of the general population of the United States. As the prevalence of other infectious diseases in Indians declined, otitis media seemed not only to persist but to be even more prominent. A causal relationship of environmental and behavioral factors of economic deprivation to otitis media had been suggested. Comparable appraisals of occurrence and geographic distribution of otitis media were not available. The natural history of otitis in Indians was undefined; middle ear effusion was thought to be uncommon.⁸¹ The two main purposes of this prospective project were 1) to develop and evaluate means that would enhance the effectiveness of treatment regimens, and 2) to investigate the association of environmental and behavioral factors with the occurrence of otitis media.⁸¹

METHODS AND PROCEDURES

Study Design. Cohorts of all children born since the beginning of the project in May 1974 were followed. The Indian Health Service, US Public Health Service, employs a uniform record system that includes an ambulatory patient care report for each patient visit. These reports, completed by the physician, were examined daily by local technicians specially trained for the otitis media project. All visits for ear disease were abstracted from the individual patient records. The technicians additionally visited the home of each infant 6 weeks after birth, then

quarterly; the technicians collected environmental data concerning the home, conducted educational programs in homes, transported patients to health care facilities, and worked in the otolaryngology clinic. Although not initially part of the study design, approximately monthly visits were made by an otolaryngologist to each reservation's hospital. The field clinics provided an opportunity for patients to be seen in consultation, for the primary care physicians to confer with the otolaryngologist, and for the otolaryngologist to monitor the quality of care (including documentation in the patient medical records). An ear microscope was used; an audiologist provided impedance audiometry and pure tone and speech audiometry in a sound-treated room.⁸¹

Study Populations, Sites, and Criteria for Otitis. Observations were made among four populations of Arizona Indians who received health services at various facilities of the Indian Health Service. Comprehensive services were provided through service units that included a general hospital of 30 or more beds, satellite clinics, and community health services. Complementary programs were operated under Indian tribal direction. The populations included in this study were members of the Hopi and Navajo tribes residing in the vicinity of the Keams Canyon Hospital, residents of selected San Carlos Apache communities near the San Carlos Hospital, and members of the Colorado River Indian tribes served by the Parker Hospital. The study sites represented a variety of climatic, physiographic, economic, and cultural factors.⁸¹

Uniform terminology and diagnostic criteria for otitis

TABLE 11. FREQUENCY DISTRIBUTION OF ENCOUNTERS FOR ACUTE SUPPURATIVE OTITIS MEDIA, BY YEAR OF LIFE

No. of Encounters	Percent of Children With Indicated Frequency of Encounters by Year of Life							
	1 (n = 2,981)	2 (n = 2,529)	3 (n = 2,094)	4 (n = 1,663)	5 (n = 1,226)	6 (n = 789)	7 (n = 427)	8 (n = 64)
0	42.1	50.0	71.6	80.9	83.9	88.8	92.8	93.7
1	23.4	25.5	19.0	14.6	13.1	8.3	6.3	3.2
2	14.9	11.4	6.3	3.6	1.9	2.1	1.0	1.6
3	8.6	6.3	1.8	0.6	0.7	0.5		1.6
4	4.2	3.4	0.7	0.1	0.3	0.1		
5	3.0	1.5	0.3		0.1	0.1		
6	1.4	0.9	0.1	0.1				
7	0.9	0.4		0.1				
8	0.6	0.2		0.1				
9	0.4	0.2						
≥ 10	0.5							

Information from reference 82.

TABLE 12. RELATION BETWEEN FREQUENCY OF ENCOUNTERS FOR OTITIS MEDIA (ACUTE AND CHRONIC) DURING FIRST 2 YEARS OF LIFE AND FROM 2 TO 5 YEARS OF AGE AMONG 1,226 CHILDREN OBSERVED FOR 5 YEARS

Encounters for Otitis in First 2 Years of Life	No. of Children	Percent of Children With Indicated Number of Encounters at 2 to 5 Years of Age			
		0	1	2	≥ 3
< 2	632	66.7	22.9	6.9	3.3
≥ 2	594	39.2	26.9	16.3	17.0

Information from reference 82.

media were followed. The criteria were reviewed periodically with the medical staff at each service unit to stress the need for consistency and to provide regular reports of project activities. Clinically "silent" otitis media was not sought in this study, but was included if identified incidentally during other health care, routine well-child evaluations, or school screenings.⁸¹

FINDINGS

From May 1974 through June 1982, data were obtained for 21,150 discrete episodes of ear disease: 76% for acute suppurative otitis media, 11% for chronic otitis media, 9% for serous otitis media, and 4% for hearing loss. More than 4,300 children were born during this time; 2,981 were followed for at least 1 year and 1,226 for 5 years or longer. Data on the children observed from birth show that a larger percentage of infants were affected and had more frequent attacks than did older children (Table 11⁸²). Of the children followed for 5 or more years, 79.5% had at least one clinical encounter for acute suppurative otitis media: about 70% of the initial attacks occurred during the first year of life, and more than 85% of the first attacks were recorded before the age of 2 years. Of initial attacks during the first year of life, 85% occurred among children from 3 to 9 months of age. Second attacks usually occurred within a few months of the first: about 85%, within 6 months. A similar pattern was apparent in the occurrence of subsequent attacks.⁸²

In the first 2 years of life, 90% of children having two or more clinical episodes of otitis media had the problem bilaterally, although not necessarily simultaneously; 99% with four or more bouts had the problem bilaterally. The rates of acute, serous, and chronic otitis among males were not significantly different from the rates among females.

Children at "high risk" of having many attacks in the first 2 years of life could be identified early by having two separate clinical encounters for otitis media, whether labelled acute or serous or chronic, before the age of 2 years. About 48% of the children at each study site thus were identified as high risk. The younger a child was when the first attack occurred, the more likely was the possibility that further attacks would occur. High risk children also had more encounters later in life: 17% of the high risk children subsequently had "persistent" otitis, ie, three or more clinical encounters of otitis from 2 to 5 years of age. In contrast, of the children having zero or one clinical encounter of otitis in the first 2 years of life, only 3.3% had three or more encounters in the next 3 years of life (Table 12⁸²). Overall, 8% of the children were at high risk for recurring otitis in the first 2 years of life and were to persist to have three or more clinical encounters of otitis in the next 3 years of life. At Parker Hospital, the rate of persistent otitis was slightly but significantly higher than at the other sites; this higher occurrence was associated with a high rate of allergic rhinitis.⁸³

The high risk and persistent patients commonly had, at one clinical encounter or another, each of the diagnostic labels: acute otitis, serous otitis, and chronic otitis. The winter seasonal exacerbation of encounters of otitis media was the same for each of the three categories of otitis and for patients living at each of the four reservations.^{82,84}

No causal association of environmental factors with otitis media could be found: factors considered were number of persons in the household, number of sleeping rooms, type of water supply and sewage disposal, type of heating and cooling, availability of electricity, method of infant feeding, distance to a health facility, and mother's education.⁸⁵

CHANGES IN HEARING STATUS OF ALASKAN NATIVES

DAVID CANTERBURY, EDD

Many articles addressing the prevalence of middle ear disease have cited the frequent occurrence of such problems in Alaskan natives. These people continue to have more hearing loss than might be found in other ethnic groups or geographic sections of the United States. Perhaps what has not been evident, however, is that there has been a shift in the prevalence of certain types of identified disorders in this population over the past three decades. Studies done as early as 1957 by Hayman and Kester⁸⁶ revealed that 53.3% of Alaskan natives showed tympanic membrane abnormalities including perforations, retractions, scarring, and inflammation. The McGrath Project in 1957⁸⁷ had similar findings in southwestern Alaskan villages. There were 546 children in this study. Eighty-six (16%) had tympanic membrane perforations. Hearing tests were done on 271 of these children, and mild hearing loss (in excess of 20 dB at one or more frequencies) was found in 25%.

In the past three decades, the hearing health care delivery system in Alaska has changed substantially. Otolaryngology service has been available since 1969 at the Alaska Native Medical Center, and this program currently serves many regions of the state with itinerant services. A system of regionalized audiology clinics provided by the state health department and the Indian Health Service serves an estimated 10,000 clients each year. Additionally, 204 native community health aides are now employed to provide primary care, even in very small villages. These developments have allowed basic changes to be made in treatment as well as preventive and rehabilitation services for the hearing impaired.

RECENT CHANGES IN HEARING STATUS

Perhaps because of the emergence of the aforementioned program initiatives over the past three decades, changes have been observed in the nature and frequency

TABLE 13. IMPEDANCE DATA FROM TESTING OF SOUTHWESTERN ALASKA HEAD START CHILDREN

	1977 to 1978 (N = 385 Ears)		1985 to 1986 (N = 361 Ears)	
	No.	%	No.	%
Normal impedance findings	219	57.0	212	58.7
Impedance consistent with middle ear effusion	48	12.5	32	8.9
Impedance consistent with negative middle ear pressure > 100 mm	82	21.0	62	17.2
Impedance indicating large canal volume and perforation	36	9.3	35	9.7
Large canal volume and patent ventilation tube	0	0.0	20	5.5

of hearing disorders occurring in Alaskan native populations. The following are some of the changes that have been noted by those involved with hearing health in Alaska. 1) Health care providers who serve this population statewide have become aware of an overall reduction in the number of chronically draining ears, even though certain geographic regions in Alaska still have a very high occurrence of this ear disease. 2) A more frequent observation of middle ear effusion in young children has been noted. This may, in fact, be the result of the use of more sensitive evaluation tools, including pneumatic otoscopy and impedance audiometry, in rural Alaska (S. Clift, MD, Chief, Ear Nose Throat Department, Alaska Medical Center, personal communication, 1985). 3) An increasing concern has developed regarding the substantial prevalence of high frequency hearing loss consistent with noise exposure or the toxic effects of prolonged middle ear infection. 4) An additional observation has been that adult Alaskan natives frequently manifest moderate to severe mixed hearing loss as they become older because of the cumulative effects of otitis, noise exposure, and aging. In attempts to quantify and validate these observations, several studies have been undertaken during the past 10 years. While there may be a temptation to generalize the results of these studies statewide, it must be remembered that Alaskan villages are often quite different from one another, and factors such as race, socioeconomic status, climate, health care access, and availability of transportation systems often result in vastly different patterns of disease from village to village. The following study results are presented only as preliminary data that appear to mark trends in hearing health status for Alaskan natives.

Kimball's⁸⁸ observation of the change in the status of high school freshmen at Mt Edgecumbe Bureau of Indian Affairs High School in southeastern Alaska seems to confirm a recent statewide decline in middle ear disease. This residential high school enrolls students from small villages statewide. During the 1975 to 1976 school year, 49% of the 201 incoming students demonstrated conductive (15-dB air-bone gap in one or more frequencies at 500 to 4,000 Hz) or mixed hearing loss (conductive loss plus a sensory loss in excess of 25 dB at 500 to 4,000 Hz). Six years later, only 13% of 112 entering students showed conductive or mixed loss and 76% had normal hearing. In each year the hearing was monitored, from 9% to 13% of the new students demonstrated high-frequency sensory loss (in excess of 25 dB at 4,000 Hz).

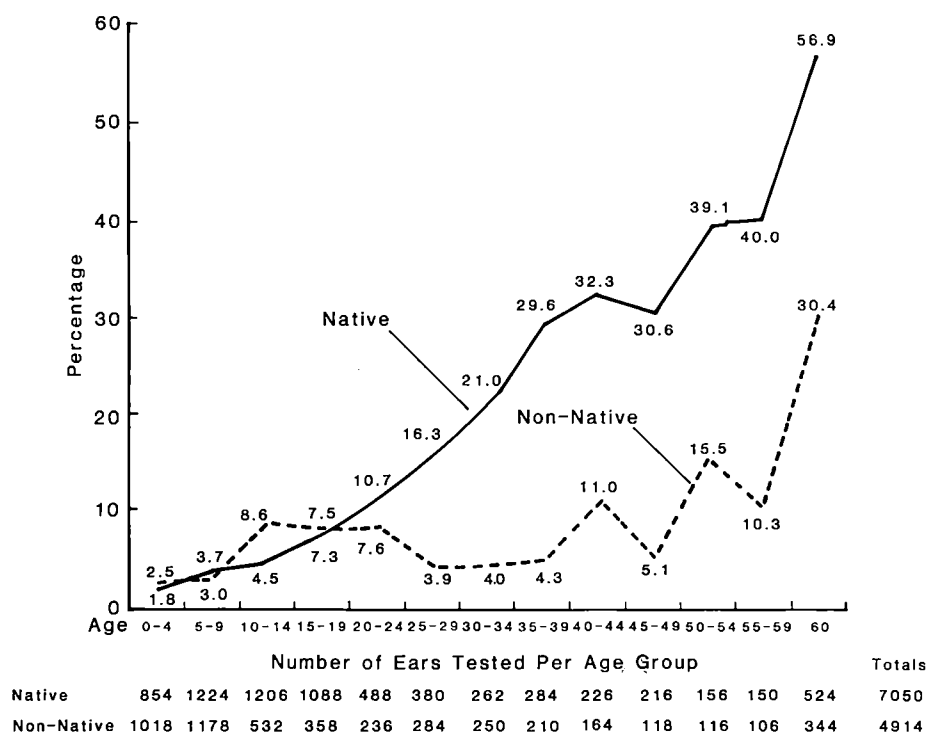
In contrast to the above findings is information col-

lected concerning the acoustic impedance testing of children enrolled in Head Start programs from small villages in the Bethel area of southwestern Alaska (Table 13). This region long has been noted for its very high prevalence of middle ear disease and has been an area in which much attention has been given to increased otologic and audiology care. The impedance data suggest that the prevalence of middle ear effusion, negative middle ear pressure, and perforations has changed only slightly during the past 8 years in this geographic region. Perforations continue to exist in about 9% of the ears of these children. Negative middle ear pressure and effusion have declined slightly in occurrence. The percentage of children with normal impedance findings essentially was unchanged. The fact that 5.5% of the ears evaluated in 1985 to 1986 had patent ventilation tubes reflects the increased attention being directed toward early surgical intervention in cases of persistent effusion. Although objective otologic data are not available for the area, it is the observation of most health care providers in the region that chronically draining ears are observed much less frequently today than 10 to 15 years ago. There currently is a village-level management and treatment program that uses native physician assistants, and this effort may well be reducing the number of complications that previously resulted from untreated middle ear disease.

One of the most recent studies was an otitis media and hearing disorder prevalence study of four separate remote villages located in different regions of the state (one Indian, two Eskimo, and one Russian-American).⁸⁹ These villages are quite different geographically and culturally, and even this four-location sample does not represent the diverse nature of the problem in Alaska adequately. The study included 1,431 subjects, or 75% of the residents of these villages. Subjects from birth to 19 years of age had 1,681 ears examined clinically by a pediatrician and an audiologist. Tympanic membrane perforations were found in 15 ears, 12 of these in Eskimo children. Notably, only one perforation was found in the 243 Indian children in this group. The Eskimo children had a 2% rate of perforation. Middle ear effusion (including acute otitis) was observed in each race group with about equal prevalence. From birth to age 4, Eskimos were found to have effusion in 23% of ears, Indians in 19%, and Russian-Americans in 22%. As expected, there was a rapid decline in this condition in older children. Acute otitis media was recorded in 10 cases (two of bilateral disease). Five cases were found in the Eskimo population and five in the Indian population. When compared with prior studies, this indicates a low prevalence of chronic and acute otitis and a relatively high rate of middle ear effusion in the villages studied. Another observation of this study was that high-frequency sensorineural hearing loss was found to occur in Eskimo and Indian boys at the early age of 10 to 14 years (approximately 6% of the ears tested) and occurs with increasing frequency with age. More than 35% of the ears of the Eskimo boys demonstrated high-frequency sensory loss by 20 to 24 years of age. These findings are consistent with those earlier cited by Kimball.⁸⁸

The impact of otitis media on these native people as they grow older has not been well studied. The clinician working with older Alaskan natives is often confronted with patients who present evidence of the cumulative effects of middle ear disease and sensory loss due to a combination of factors including noise exposure, toxic effects of

Fig 3. Moderate to profound hearing loss in native and nonnative Alaskans.



prolonged otitis, and presbycusis. In an effort to document the scope of the problem, the audiometric findings of 5,986 people seen in audiology clinics in 1979 and 1980 were reviewed (D. Canterbury et al, unpublished data, 1981). Analysis of this information should be done with the clear realization that these are not prevalence data but an examination of one parameter of test findings obtained from clients seen in our clinics in 1 year. Fifty-nine percent were Alaskan natives and 41% were nonnatives. The two categories were compared by age group for severity of hearing loss. The results suggest far greater occurrence of moderate (41-dB pure tone average) to profound hearing loss in the native population than in the nonnatives. The difference begins to manifest at about 20 years of age, and the margin between the two racial groups widens with age. While all hearing loss is of concern, hearing loss of this

degree can present a substantial handicap to individuals so affected (Fig 3).

DISCUSSION

Currently available data on hearing loss and otitis media indicate that a more comprehensive study should be undertaken in certain subgroups within the Alaskan native population in order to document their hearing and middle ear status more precisely and to determine their treatment and rehabilitation needs. These groups are 1) children, birth to age 4, with middle ear effusion; 2) residents of specific geographic areas such as southwestern Alaska; 3) teenagers who are demonstrating an early onset of high-frequency hearing loss; and 4) adults who exhibit moderate to profound degrees of hearing loss with advancing age.

OTITIS OCEANIA: MIDDLE EAR DISEASE IN THE PACIFIC BASIN

GREGORY DEVER, MD; SYLVAN E. STOOL, MD; SCOTT MANNING, MD; JEAN STEWART, MA, MPH

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Among the Pacific islanders the epidemiology of otitis media is not well described, but generally is thought in certain island communities to be excessive.⁹⁰ Unlike in select indigenous Pacific rim populations of North America,^{91,92} Australia,^{93,94} and New Zealand,⁹⁵ there are few studies concerning middle ear disease in the Pacific area, including the American flag territories in Micronesia,⁹⁶⁻⁹⁸ and Polynesia.⁹⁹ However, in spite of limited documentation, some island communities, particularly in western Micronesia, regard chronic middle ear disease and its sequelae as the most common handicapping condition among their children.⁹⁰ To better document the preva-

lence of middle ear disease in the region, studies have been initiated in a clinical training program utilizing a disease severity scale of tympanic membrane findings to standardize observations and facilitate the recording and reporting of information.

BACKGROUND

The United States island jurisdictions of Micronesia include the Territory of Guam and the Trust Territory of the Pacific Islands, which comprises the Commonwealth of the Northern Marianas, the Republics of Belau and the Marshall Islands, and the Federated States of Micronesia

TABLE 14. REVISED OTITIS MEDIA DISEASE SEVERITY SCALE

Class	Severity Scale
0	Inability to visualize (ie, obstructing cerumen, atresia)
1	Neutral, white, mobility normal, translucent
2	Neutral or slight retraction; white or pink; mobile or slight decrease; slight tympanosclerosis; slight opacity
3	Retracted, healed perforation; extensive tympanosclerosis; decreased mobility
4	Bulging pink, grey, amber, red; decreased mobility
5	Severe retraction; markedly decreased mobility
6	Perforation
FB	Foreign body
Class 1 — normal tympanic membrane, classes 2 and 3 — past mild disease, classes 4 to 6 — active disease requiring therapy.	

(Yap, Truk, Pohnpei, and Kosrae). In the Trust Territory, a developing area in which a sparse population base of 140,000 live on small islands scattered over a Pacific expanse of 3 million square miles, access to primary care is variable and at times episodic or unavailable. Infectious disease is still the leading cause of death in the Federated States of Micronesia and the Marshall Islands, and infant mortality is excessive throughout the region.^{100,101} Provision of comprehensive primary health care is frustrated by the logistics of providing services to remote island communities and complicated by scarce resources and epidemics of diarrheal diseases, tuberculosis, and malnutrition.

In the Trust Territory, middle ear disease and its sequelae generally are recognized by local and visiting health professionals to be of near-epidemic proportions.⁹⁰ However, reliable middle ear disease statistics are scarce.

1. The active Crippled Children's Services (CCS) registry for the Trust Territory for 1976 and 1977 indicates that ear, nose, and throat problems represented 25% of the total CCS caseload. It should be noted, however, that most cases were treated but not reported by the registry.¹⁰²

2. In 1981, in the Republic of Belau, 160 Head Start children were examined. Overall, 19.3% of the children had evidence of active middle ear disease, and 10.6%, disease with perforations. Subtracting those children with obstructing cerumen, of the 114 children whose tympanic membranes were examined adequately, 33% had active disease, with 16% evidencing perforations.

3. In a 1982 hearing screening of Belau Head Start children, 65% of 118 children failed the screening, and 44% of the total screened population was eventually certified as hearing-handicapped.⁹⁹

4. A second Belau Head Start hearing screening was performed in 1983 (J. Stewart, unpublished observations, American Speech-Language-Hearing Association meeting, San Francisco, 1984). Of the 81 children (approximately one fourth of the total screened) who were tested comprehensively because they had failed the initial screening, 22% had perforations.

5. In Yap State of the Federated States of Micronesia, extensive school health surveys were completed in grades 1, 4, and 8 from 1981 to 1984. The yearly perforation point prevalences were, respectively, 3.5%, 6.4%, 5.0%, and 3.0%, with an average of 4% of the 2,264 children screened over the 4 years (personal communication, C. D. Evans, Yap School Screening, 1985).

TABLE 15. MICRONESIA OTITIS MEDIA PREVALENCE RESULTS

	Pohnpei 1985	Yap 1986	Belau 1986
Well-baby clinics	(n = 56)	(n = 15)	
Tympanic membranes	78	24	—
% Perforations (class 6)	1	13	—
% Active disease (classes 4-6)	46	42	—
Head Start children	(n = 35)	(n = 86)	(n = 65)
Tympanic membranes	46	154	127
% Perforations (class 6)	0	3	9
% Active disease (classes 4-6)	28	9	16
Elementary school children	(n = 299)	(n = 526)	(n = 531)
Tympanic membranes	458	1,001	1,003
% Perforations (class 6)	3	2	8
% Active disease (classes 4-6)	14	3	10
Secondary schools 1985			
Pohnpei High School	(n = 280)		
Tympanic membranes	553		
% Perforations (class 6)	2		
% Active disease (classes 4-6)	3		
Pohnpei agricultural	(n = 109)		
Tympanic membranes	203		
% Perforations (class 6)	3		
% Active disease (classes 4-6)	3		

6. In 1985, 115 Yapese children 3 to 5 years of age were screened.⁹⁸ Of these, 17.4% had active otitis media and 5.2% had perforations (personal communication, J. Flear, Yap School Screening, 1985).

7. In the Republic of the Marshall Islands, in a 1982 Head Start screening of 69 outer atoll children, 60.3% evidenced active middle ear disease, with 2.8% manifesting perforations (G. Dever, unpublished data).

METHODS

In 1985 the first of four clinical training programs in level-appropriate surgical, medical, and screening techniques for the diagnosis and treatment of middle ear disease was initiated in Micronesia. As part of the Micronesia Otitis Media Training Project, point prevalence studies were integrated into the project to better define the extent of middle ear disease in the region. To standardize a uniform diagnostic criterion and to facilitate a precise reporting of clinical findings adjusting for ears not adequately visualized, an otitis media disease severity scale for tympanic membranes was developed, implemented, and revised (Table 14).

Overall, during 1985 and 1986 the Micronesia Otitis Media Training Project trained over 45 primary health care workers and performed almost 70 surgical procedures while training three Micronesian physicians in the current surgical techniques. Additionally, two otolaryngologists screened 2,002 Micronesian infants, children, adolescents, and adults using the disease severity scale in training projects in Pohnpei, Yap, and Belau. The screeners both used 3.5-V halogen diagnostic pneumatoscopes. To ensure continuity, the second otolaryngologist was certified in the use of the revised scale by the first observer.

RESULTS

Point prevalence studies in over 2,000 Micronesian children and adults (Table 15) have revealed very excessive rates of active disease (classes 4 to 6), particularly in well

babies in Pohnpei⁹⁸ and Yap, with 46% and 42%, respectively, of the total tympanic membranes displaying active disease. Forty-six percent of the Pohnpeian and 33% of the Yapese well babies had active otitis media requiring therapy.

In Head Start children, generally 5 years of age, the point prevalences of active disease ranged from 28% of tympanic membranes in Pohnpei and 16% in Belau to 9% in Yap. The prevalences of active disease among elementary school children ranged from a high of 14% of tympanic membranes in Pohnpei, to 10% in Belau, to a low of 3% in Yap. Continuing the general trend of decreasing disease with age, the high school students in both secondary schools in Pohnpei had a prevalence of otitis media of 3% of observed tympanic membranes.

Also very remarkable were the high and variable point prevalence rates of perforations (class 6) in Head Start children, particularly in Belau (9%), whereas no perforations were diagnosed in the Pohnpei Head Start children. High perforation prevalences in the elementary school children also were noted in Belau in 8% of the tympanic membranes and in 3% and 2% of the tympanic membranes in comparable Pohnpeian and Yapese school children, respectively. This corresponds to 13% of the Belauan, 5% of the Yapese, and 4% of the Pohnpeian elementary school children screened. The above perforation prevalences are generally consistent with the observations noted

previously in Yap (personal communication, C. D. Evans and J. Flear, Yap School Screening, 1985) and Belau (G. Dever, unpublished data). Additionally, of the 389 high school and agricultural school students examined in Pohnpei, about 2% of their tympanic membranes were perforated.

DISCUSSION

The Micronesian peoples not only are separated by an ocean expanse equal in area to the continental United States, but they have dissimilar languages and customs. However, commonalities include their relative isolation, stable climate, and variable access to primary health care. Although middle ear disease and perforation point prevalences vary throughout the region, the tympanic membrane perforation frequencies in children from Belau (8% to 9%), Yap (3% to 13%), and Pohnpei (2% to 4%) are excessive and are comparable regionally to the higher tympanic membrane perforation prevalences noted among children of Australian aborigines (2% to 36%),^{93,94} among New Zealand Maoris (5% to 10%),⁹⁵ and among 3% of urban children from the Papua New Guinea Highlands.¹⁰³ Also noted is the very excessive active disease occurrence in the tympanic membranes of the well babies of Pohnpei (46%) and Yap (42%). As the Micronesia Otitis Media Project continues, additional prevalence information from Micronesia (and Polynesia) will assist in better defining the extent of the problem in the region and in assessing the efficacy of clinical training programs.

EPIDEMIOLOGY OF OTITIS MEDIA IN BOSTON CHILDREN OBSERVED FROM BIRTH TO 7 YEARS OF AGE

JEROME O. KLEIN, MD; DAVID W. TEELE, MD; BERNARD ROSNER, PhD;
CAROLE ALLEN, MD; LORNA BRATTON, MD; GILBERT FISCH, MD;
PETER STRINGHAM, MD; SYDNEY STAROBIN, MD; LLOYD TARLIN, MD

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To determine the epidemiology of otitis media during the first 7 years of life, pediatricians in health care centers in Greater Boston enrolled 1,069 children at birth or before 3 months of age, beginning May 1975. The participating programs were an urban health center in East Boston and suburban private practices in Holliston and Framingham, Mass. At each visit for acute medical or well-child examination, a record of the history, physical examination, and otoscopic examination was made. An episode of acute otitis media was defined for the purpose of this study by the presence of effusion in the middle ear in a child with one or more clinical signs of illness, including otalgia, ear-tugging, fever, irritability, lethargy, anorexia, vomiting, or diarrhea. We defined otitis media with effusion as liquid in one ear or both ears of a well child. All physicians participating in the study were trained in otoscopic examination and pneumatoscopy and were tested during the program to minimize interobserver differences. A preliminary report of the epidemiology of otitis media in Boston children to 3 years of age was presented at the Second International Symposium on Recent Advances in Otitis Media with Effusion.⁵⁹ The purpose of this report is to provide information on the epidemiology of otitis media in Boston children from birth

to 7 years of age. A more complete report was recently published.¹⁰⁴

Of the 1,069 children enrolled at birth or prior to 3 months of age, 877 were still active in the practices at 1 year, 698 were active at 3 years, and 498 (46.5% of those enrolled at birth) were still active at 7 years. "Active in the practice" was defined as at least one visit to the practice after the specific age used for analysis. Attrition was usually due to parents' moving to another area or to parents' changing pediatricians. The proportion of active children was approximately the same in the urban health center and private practices. Most children were white (96.8%). A majority of households using the urban health center were of low socioeconomic status; conversely, most households using the suburban private practices were of high socioeconomic status. Approximately one half the children in each group had one or more siblings, and approximately one third of the siblings had a history of chronic otitis media. Breast-feeding was used by 37% of mothers of high socioeconomic status and 20% of mothers of low socioeconomic status.

The age-specific incidence of acute otitis media for each of the 7 years of observation is shown in Table 16. The

TABLE 16. AGE-SPECIFIC INCIDENCE OF EPISODES OF ACUTE OTITIS MEDIA DURING EACH YEAR OF OBSERVATION OF 498 BOSTON CHILDREN OBSERVED FROM BIRTH TO 7 YEARS OF AGE

Episodes of AOM	Year of Life						
	1	2	3	4	5	6	7
0	38	41	59	58	58	63	70
1	31	29	24	23	26	24	20
2	14	20	10	11	9	8	6
3+	17	10	7	8	7	5	4

AOM — acute otitis media.

peak incidence of acute otitis media occurred in the first year of life. By 7 years of age, 93% of children had had at

least one episode of acute otitis media and 74% had had three or more episodes. The mean number of episodes of acute otitis media was highest during the first year — 1.2 — with a decline to 0.4 in the seventh year.

The mean duration of middle ear effusion following each episode of acute otitis media was 23 days. The mean duration was highest in the first year of life — 29.4 days — decreasing to 14.3 days in the seventh year. The mean and median duration of middle ear effusion during the first 7 years of life for the cohort of 498 children were 152 and 117 days, respectively.

Significantly increased risk for acute otitis media was associated with being male, not being breast-fed, having a sibling with severe or recurrent otitis media, and early occurrence of acute otitis media.

INCIDENCE, PREVALENCE, AND NATURAL HISTORY OF OTITIS MEDIA IN CHILDREN IN PITTSBURGH

MARGARETHA L. CASSELBRANT, MD, PhD; LEON M. BROSTOFF, MD; ERDEM I. CANTEKIN, PhD; VICTORIA M. ASHOFF, MA; CHARLES D. BLUESTONE, MD

INTRODUCTION

The purpose of the present study was to study the incidence and prevalence of otitis media with effusion and high negative pressure in children 2 to 12 years of age in the Pittsburgh area.

MATERIAL AND METHODS

Two groups of children were examined; the first group of 103 children, 2 to 5 years of age, attended a nursery school in Verona, a suburb of Pittsburgh^{105,106}; the second group consisted of 111 schoolchildren, 5 to 12 years of age, in the Falk Elementary School in Pittsburgh.¹⁰⁶ The preschool children were examined from September 1981 through August 1983, and the schoolchildren from September 1984 through May 1985.

At monthly intervals, the principal investigator and a nurse practitioner, both validated in otoscopy,¹⁰¹ a nurse trained in middle ear acoustic impedance measurements, and an audiologist visited the school. At each visit, the children were examined for the presence or absence of otitis media with effusion and upper respiratory (tract) infection (URI). A URI was defined as the presence of rhinorrhea, edema, or erythema of the nasal mucosa with some degree of nasal obstruction. The diagnosis of middle ear effusion was made with an algorithm that combines the independent findings of pneumatic otoscopy, tympanometry, and acoustic reflex measurement.¹⁰⁷ Children were classified at each examination into one of three categories according to the status of the worse ear: normal, otitis media with effusion, or high negative middle ear pressure (negative pressure equal to or less than -200 mm H₂O in an effusion-free ear). The data were analyzed by the same methods as previously reported.¹⁰⁵

A scoring system was developed to summarize each child's experience with otitis media with effusion and high negative pressure over a 1-year period. Normal ears were given a score of 0; ears with high negative pressure, a score

of 1; and ears with otitis media with effusion, a score of 2. Based on the worse ear at each visit, a yearly score was calculated for each child. This yearly score was then adjusted (normalized) by dividing by the number of visits and multiplying by 12 to reflect the number of observations made for each child.

RESULTS

The cumulative incidence of the first episode of otitis media with effusion is shown in Fig 4. The two populations were significantly different ($p < .001$); 66% of the preschoolers were judged to have effusion in at least one ear, compared to 22% of the school-age children. In both groups of children, about 90% of the children with otitis media with effusion had the effusion by February. A second episode of otitis media with effusion was documented in 36% of the preschool children, as compared to 12% of the school-age children.

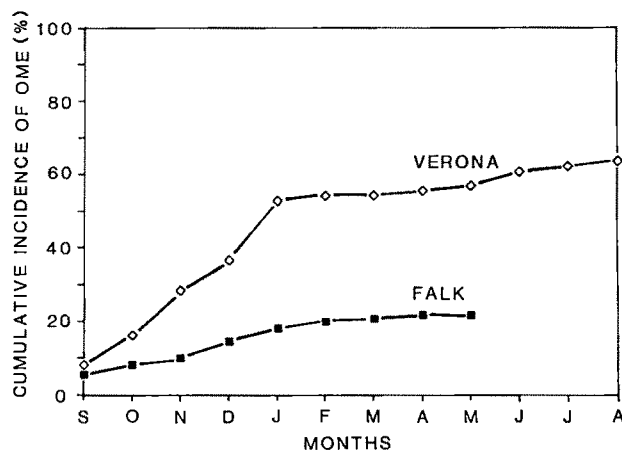


Fig 4. Cumulative incidence of first episode of otitis media with effusion (OME).

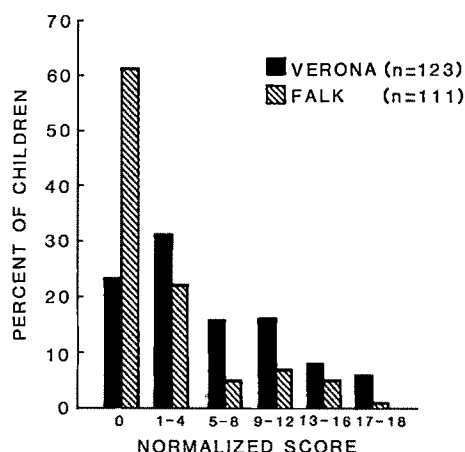


Fig 5. Frequency distributions of children according to their normalized score.

Most episodes of otitis media with effusion were of brief duration in both populations. Over 60% of the episodes cleared without intervention after 1 month and 80% after 2 months. After 3 months of effusion, parents were informed of the child's condition, and intervention was advised.

The middle ear status showed a seasonal variation that was especially marked in the preschool children. In September, about 80% of the younger children had bilateral normal ears, while in January, only 45% had normal ears. The highest point prevalence of otitis media with effusion, 33%, occurred in January in this group. In the older children, the peak point prevalence of otitis media with effusion was 11% and also occurred during the winter months.

In addition to this seasonal variation, there was a relationship between URI and otitis media with effusion. In the preschool children during a URI, 32% of the ears had effusion, whereas only 11% had otitis media with effusion when there was no URI. In the school-age children, 14% of the ears had otitis media with effusion when the child had a URI, as opposed to 2% when the child did not. The

seasonal variation in URI episodes reflected the seasonal distribution of otitis media with effusion.

The frequency distributions of children according to their normalized score are shown in Fig 5. A score of 0 indicates that the child did not have a documented episode of otitis media with effusion or high negative pressure during the study period. Sixty-two percent of the schoolchildren and only 23% of the younger children had a score of 0. A score between 1 and 4, suggesting a few months of either otitis media with effusion or high negative pressure, was found in 20% of the schoolchildren and 30% of the preschool children. Approximately 50% of the younger children and 20% of the schoolchildren had a score of 5 or higher.

The relationship between age and the prevalence of otitis media with effusion and high negative pressure was investigated by calculating the average normalized score for each age from 2 to 12 years. Because of the consistency of the scores in children younger than 6 years and older than 6 years, we calculated a group average for these two age groups. For the younger group, the average score was 5.9, which was significantly higher than the score of 1.73 for the older age group ($p < .001$). Furthermore, the possible confounding effects of two different school populations on this age incidence were investigated by comparing the 5-year-old children who attended both schools. Interestingly, the average normalized scores in these two different populations were the same: 5.6 and 5.4, in the preschool children and schoolchildren, respectively.

CONCLUSIONS

These findings show that otitis media with effusion and high negative middle ear pressure in 2- to 12-year-old children are common. The incidence decreases with age, and the period between 5 and 6 years seems to be critical. Most episodes of otitis media with effusion were short and resolved spontaneously within 3 months. There is a strong seasonal variation, with the highest prevalence of otitis media with effusion and high negative pressure during the winter months. This variation may be partially caused by a parallel seasonal variation in URI.

PROGNOSTIC FACTORS IN OTITIS MEDIA WITH EFFUSION

ELLEN M. MANDEL, MD; HOWARD E. ROCKETTE, PhD; MARCIA KURS-LASKY, MS;
CHARLES D. BLUESTONE, MD

INTRODUCTION

Otitis media with effusion in the general childhood population is often undetected, resolving spontaneously and recurring frequently, as shown in screening studies of preschool and school-age children.^{105,106} However, once a child is identified as having middle ear effusion, the concern becomes what will happen to that effusion over a specified time period if left untreated. The objective of this paper is to identify patient characteristics that will help predict which patients are likely to clear their effusion. These prognostic factors associated with otitis media with effusion were investigated by use of information obtained from clinical trials conducted at the OMRC at Children's Hospital of Pittsburgh.

Prognostic factors were investigated in placebo-treated subjects enrolled in randomized, controlled double-blinded studies of medical therapy for otitis media with effusion: one trial from July 1978 to June 1981, evaluating the efficacy of a decongestant/antihistamine combination for otitis media with effusion (Decongestant-Antihistamine Study)¹⁰⁸ and one trial from July 1981 to October 1984, evaluating the efficacy of antibiotic therapy for otitis media with effusion (Antibiotic Study).¹⁰⁹ Eligibility criteria were similar for these two trials: subjects were between 7 months and 12 years of age, had otitis media with effusion in at least one ear as determined by a validated otoscopist, had no symptoms of acute otitis media (ie, fever, otalgia, or irritability) or purulent rhinorrhea, had no

TABLE 17. PROGNOSTIC FACTORS FOR SELECTED POPULATION CHARACTERISTICS

Characteristic		At 2-Week End Point						At 4-Week End Point					
		DA Placebo			AB Placebo			DA Placebo			AB Placebo		
		Effusion-Free			Effusion-Free			Effusion-Free			Effusion-Free		
		%	No.	RR	%	No.	RR	%	No.	RR	%	No.	RR
Race	White	11.0	163	.61	12.0	92	.77	20.1	159	.64	12.2	90	.98
	Nonwhite	18.0	61	1.63	15.6	32	1.31	31.6	57	1.57	12.5	32	1.02
Age	7-23 mo	13.2	68	1.03	11.1	36	.82	25.9	58	1.17	10.0	40	.75
	2-5 yr	10.9	101	.74	16.9	65	2.00	20.8	106	.82	14.5	62	1.45
	6-12 yr	16.4	55	1.38	4.3	23	.29	25.0	52	1.11	10.0	20	.79
Duration	0-3 wk	26.3	38	2.58*	29.4	17	2.86	35.5	31	1.68	17.6	17	1.54
	4-8 wk	10.9	46	.81	10.5	19	.79	24.4	41	1.07	16.7	18	1.44
	>8 wk	9.0	67	.61	9.1	44	.61	15.2	79	.55*	8.9	45	.62
	Unknown	11.0	73	.79	11.4	44	.83	26.2	65	1.20	11.9	42	.95
Previous antibiotic	No	12.0	92	.88	9.8	41	.68	24.2	91	1.08	12.2	41	.99
	Yes	13.6	132	1.14	14.5	83	1.48	22.4	125	.93	12.3	81	1.01
Sex	F	10.0	90	.67	18.2	44	1.82	19.3	83	.75	8.7	46	.60
	M	14.9	134	1.49	10.0	80	.55	25.6	133	1.33	14.5	76	1.66
Laterality at entry	Unilateral	23.1	65	2.62†	8.8	34	.61	36.8	68	2.18†	19.4	31	1.96
	Bilateral	8.8	159	.38†	14.4	90	1.64	16.9	148	.46†	9.9	91	.51
History of ear disease	No	14.6	48	1.16	9.1	11	.69	35.4	48	1.84*	20.0	10	1.72
	Yes	12.6	175	.86	13.3	113	1.46	19.3	166	.54*	11.6	112	.58
Season	Winter	14.5	76	1.19	10.6	47	.75	21.5	65	.90	13.3	45	1.14
	Spring	14.5	62	1.18	11.8	34	.88	28.6	63	1.37	12.1	33	.98
	Summer	15.4	26	1.22	26.7	15	2.42	18.2	33	.76	15.4	13	1.29
	Fall	8.3	60	.57	10.7	28	.79	21.8	55	.92	9.7	31	.73
URI at entry	No	17.6	108	2.18	14.3	84	1.39	22.0	109	.81	13.6	81	1.36
	Yes	8.1	62	.46	10.3	39	.72	27.3	55	1.24	10.0	40	.74
URI at 2 weeks	No	17.6	119	3.22*	16.9	89	5.90	27.9	122	2.20*	13.3	90	1.42
	Yes	5.5	73	.31*	2.9	35	.17	12.7	71	.46*	9.4	32	.70
History of ear disease, parents	No	14.1	163	1.29	11.1	81	.68	24.8	161	1.33	11.8	76	.91
	Yes	10.9	55	.77	16.3	43	1.47	18.8	48	.76	13.0	46	1.10
Fluid level or bubbles, R ear	Absent	12.2	147	.38*	10.7	84	.21†	19.7	142	.46*	19.3	88	.84
	Present	32.3	31	2.63*	50.0	18	4.67†	43.3	30	2.20*	23.1	13	1.20
Fluid level or bubbles, L ear	Absent	15.1	159	.63	19.3	88	.77	27.2	151	1.81	20.9	91	1.04
	Present	23.8	21	1.58	25.0	12	1.29	15.0	20	.55	20.0	10	.96
SRT, R ear, at entry	<25 dB	21.0	62	2.19	23.1	39	6.23	27.9	61	1.77	26.5	34	3.57
	≥25 dB	9.6	73	.46	3.7	27	.16	15.8	76	.57	7.4	27	.28
SRT, L ear, at entry	<25 dB	17.5	57	1.35	35.3	34	3.53*	25.9	54	1.10	40.0	30	5.80†
	≥25 dB	13.0	69	.74	10.0	30	.28*	23.5	68	.91	6.9	29	.17†

DA — decongestant-antihistamine, AB — antibiotic, RR — relative effusion-free ratio, URI — upper respiratory tract infection, SRT — speech reception threshold.

*Significance at $p < .05$.

†Significance at $p < .01$.

history of tonsillectomy, adenoidectomy, or tympanostomy tube insertion, had no congenital craniofacial malformations, Down syndrome, asthma, or seizure history, and had no sensorineural hearing loss. In both trials, subjects were seen at entry and at 2 weeks and 4 weeks following entry for pneumatic otoscopy, tympanometry, and audiometry. Prognostic factors for the presence or absence of otitis media with effusion were investigated at the 2-week and 4-week visits. In tabulating the outcome at 2 weeks, only visits occurring between 11 and 17 days from entry were included; similarly, only visits occurring between 21 and 35 days after entry were included in the 4-week outcome. Patients receiving antibiotic treatment for intercurrent disease prior to these end points were excluded from the analysis. The relative effusion-free ratio was used and defined as the ratio of the probability of being effusion-free with the factor present to the probability of being effusion-free with the factor absent.

Statistical significance was determined for dichotomous variables by use of a χ^2 statistic corrected for continuity. For those variables classified into more than one category, the relative risks and significance levels presented in Table 17 were computed by comparing each level of the variable to the remainder of patients. In addition, for the polychotomous variables, a test for trend was used if the variable was ordered (age or duration); for unordered variables (season), a higher degree of freedom χ^2 statistic was used.

Because of the possibility of identifying a false prognostic factor when a large number of comparisons are made on a single data set, we have summarized the results of the two data sets separately so that the consistency of the identified prognostic factors can be compared. Thus, we have viewed the placebo group of the Antibiotic Study as an opportunity to confirm factors identified as prognos-

tic in the Decongestant-Antihistamine Study.

The data from the 2-week visit of 224 subjects in the Decongestant-Antihistamine Study and 124 subjects in the Antibiotic Study were available for analysis. As seen in Table 17, duration of effusion at entry was statistically significant in the Decongestant-Antihistamine Study: those subjects whose duration of effusion at entry was less than 4 weeks were more likely to be effusion-free 2 weeks later than were subjects whose duration of effusion was longer or was unknown. This was true also for subjects in the Antibiotic Study, but did not reach statistical significance (test for trend, $p = .07$). Symptoms of an upper respiratory tract infection at entry had no significant prognostic value in the Decongestant-Antihistamine Study, but having an upper respiratory tract infection at the time of the 2-week visit was linked to subjects' having effusion at that visit. Although it did not reach statistical significance in the Antibiotic Study, the trend was the same ($p = .06$). Laterality of effusion at entry (unilateral versus bilateral) was an important factor in subjects in the Decongestant-Antihistamine Study, as subjects with bilateral effusions at entry were more likely to have persistent effusion at 2 weeks than subjects with unilateral effusion. However, in the Antibiotic Study, laterality of effusion at entry was not related to outcome; surprisingly, subjects with unilateral disease were more likely to have persistent effusion at 2 weeks, although this was not statistically significant ($p = .61$). The presence of fluid levels or bubbles portended a favorable outcome at 2 weeks in both studies, but reached statistical significance only for the right ear. Hearing at entry also was linked to outcome: subjects for whom speech reception thresholds (SRTs) were obtained were more likely to be effusion-free at 2 weeks if the SRT was less than 25 dB. However, this was statistically significant only in the Antibiotic Study.

The relationship of these factors to outcome was investigated in 214 subjects in the Decongestant-Antihistamine Study and 122 subjects in the Antibiotic Study at the 4-week end point (Table 17). Again, subjects whose duration of effusion at entry was less than 4 weeks were more likely to be effusion-free. Upper respiratory tract infection

at entry had no prognostic value for the following 4 weeks, but symptoms at the time of observation were related to persistent effusion, although statistically significant only in the Decongestant-Antihistamine Study. Laterality at entry was again prognostic in the Decongestant-Antihistamine Study, with those subjects with unilateral effusion more likely to be effusion-free, and the trend was the same in the Antibiotic Study. Fluid levels or bubbles seen behind the tympanic membrane of the right ear and hearing level at entry were also again prognostic. At 4 weeks, unlike at 2 weeks, a history of previous ear disease correlated with a poorer outcome than if there were no previous problems known. At neither the 2-week nor the 4-week end point was age significantly related to outcome.

For the majority of variables, the prognostic importance of variables in the Decongestant-Antihistamine Study was confirmed by the Antibiotic Study. Duration of effusion, laterality of disease at entry, fluid level or bubbles, and hearing level at entry all appear to be related to the resolution of fluid during the first month after entry into the study. Although not a prognostic factor, the presence of an upper respiratory tract infection at the time of visit is associated with presence of otitis media with effusion.

In addition, our investigation has identified several general problems that are encountered in studies attempting to identify prognostic factors for otitis media with effusion. First, whether a factor is prognostic depends on the outcome measurement specified. Previous history of ear disease appeared prognostic at 4 weeks but not at 2 weeks. At another point in time, yet other factors might show some relationship to outcome. Also, small studies may fail to identify prognostic factors because of poor statistical power. The placebo group in the Antibiotic Study was slightly more than half the size of the placebo group in the Decongestant-Antihistamine Study, and some factors may have failed to achieve statistical significance in part because of the smaller sample size. Studies with fewer than 100 patients per treatment arm have a large probability of failing to detect prognostic factors with relative effusion-free ratios as high as 2.

PROGNOSTIC FACTORS IN NONSEVERE ACUTE OTITIS MEDIA

MARGARETHA L. CASSELBRANT, MD, PHD; PHILLIP H. KALEIDA, MD; MARCIA KURS-LASKY, MS;
HOWARD E. ROCKETTE, PHD; CHARLES D. BLUESTONE, MD

Acute otitis media is a common disease in infants and children, with a high recurrence rate, especially during the early years of life.^{59,61,63}

The objective of this paper is to identify characteristics that will help predict the patients with acute otitis media who are likely to clear their middle ear effusion and those likely to develop a recurrent episode. These prognostic factors were investigated by use of information from a randomized, double-blind, placebo-controlled clinical trial that evaluated 1) the efficacy of amoxicillin (versus placebo in children with "nonsevere" acute otitis media; and 2) the efficacy of antimicrobial therapy (amoxicillin) or myringotomy, or both, for "severe" episodes. The study was conducted at the OMRC and in a suburban private pediatric office in Upper St Clair, Pa, from May 1981 through August 1985.

Children 7 months to 12 years of age were eligible for the study if they had no history of tonsillectomy or adenoidectomy, tympanostomy tube insertion, penicillin allergy, medical problem disorder, congenital craniofacial malformation, Down syndrome, or sensorineural hearing loss. The subjects were stratified according to age and history of acute otitis media in the previous year and then were randomized into different treatment groups. A treatment regimen was assigned that specified consistent treatments for episodes of nonsevere and severe otitis media, respectively, for a 1-year period. For this report, prognostic factors were investigated only in the "placebo-treated" children who had a nonsevere episode of acute otitis media at entry. The symptoms of nonsevere disease were an oral temperature of $<39^{\circ}\text{C}$, mild otalgia or irritability with ear pulling in an infant, and absence of severe malaise or toxicity. The otoscopic signs of acute otitis media were

TABLE 18. PROGNOSTIC FACTORS FOR BECOMING EFFUSION-FREE

Characteristic	At 2 Weeks			At 6 Weeks		
	%	No.	RR	%	No.	RR
Race						
White	37.4	155	1.35	52.3	109	1.18
Nonwhite	27.8	18	.74	44.4	18	.85
Age						
< 2 yr	27.5	80	.62*	47.3	55	.87
2-5 yr	37.5	72	1.05	50.9	55	.99
6-12 yr	66.7	21	2.07†	64.7	17	1.32
No. of AOM episodes (prior year)						
0	42.4	66	1.30	53.5	43	1.07
1-2	36.8	76	1.02	55.9	59	1.19
≥ 3	22.6	31	.57	36.0	25	.66
Site						
OMRC	29.2	48	.74	42.5	40	.77
USC	39.2	125	1.34	55.2	87	1.30
Sex						
M	26.1	92	.54†	47.9	73	.86
F	48.1	81	1.85†	55.6	54	1.16
Laterality of effusion at entry						
Unilateral	45.7	81	1.62*	67.8	59	1.84†
Bilateral	28.3	92	.62*	36.8	68	.54†
Laterality of signs at entry						
None	36.4	66	1.00	52.1	48	1.03
Unilateral	38.7	75	1.12	54.5	55	1.12
Bilateral	31.3	32	.83	41.7	24	.78
Symptoms at entry						
No	32.1	28	.86	41.2	17	.78
Yes	37.2	145	1.16	52.7	110	1.28
Season at entry						
Winter	40.0	55	1.15	46.3	41	.87
Spring	38.3	47	1.07	60.0	30	1.24
Summer	44.0	25	1.25	68.4	19	1.42
Fall	26.1	46	.65	40.5	37	.73

RR — relative effusion-free ratio, AOM — acute otitis media, OMRC — Otitis Media Research Center, USC — Upper St Clair.

*Significance at $p < .05$.

†Significance at $p < .01$.

erythema or white opacification of the tympanic membrane, or both, accompanied by fullness or bulging and impaired mobility. For this report, the child must have had such symptoms, signs, or both, of acute otitis media to have been considered as having had a nonsevere episode.

The study design required that a child be seen 2 weeks after the initial diagnosis and then at monthly visits. Therefore, prognostic factors were investigated for the presence or absence of effusion at the 2- and 6-week end points and for recurrence of acute otitis media by the 6-week end point.

In tabulating the outcome at 2 weeks, a visit was included only if it occurred between 11 and 17 days after initial diagnosis. For the 6-week end point, a visit was counted only if it occurred between 35 and 49 days. Patients were excluded if they had received other antimicrobial therapy (for any reason) or a myringotomy. The relative effusion-free ratio was defined as the ratio of the probability of being effusion-free with the factor present to the probability of being effusion-free with the factor absent.

Statistical significance was determined for dichotomous variables by use of a χ^2 statistic corrected for continuity.

TABLE 19. PROGNOSTIC FACTORS FOR DEVELOPING RECURRENCE OF ACUTE OTITIS MEDIA

Characteristic	By 6 Weeks		
	%	No.	RR
Race			
White	47.6	124	1.81
Nonwhite	26.3	19	.55
Age			
< 2 yr	53.7	67	1.46
2-5 yr	40.7	59	.85
6-12 yr	23.5	17	.49
No. of AOM episodes (prior year)			
0	37.5	48	.77
1-2	47.7	65	1.13
≥ 3	50.0	30	1.15
Site			
OMRC	37.8	45	.79
USC	48.0	98	1.27
Sex			
M	45.1	82	1.02
F	44.3	61	.98
Laterality of effusion at entry			
Unilateral	53.0	66	1.41
Bilateral	37.7	77	.71
Laterality of signs at entry			
None	51.9	54	1.28
Unilateral	45.2	62	1.02
Bilateral	29.6	27	.61
Symptoms at entry			
No	61.9	21	1.48
Yes	41.8	122	.68
Season at entry			
Winter	48.9	47	1.15
Spring	28.6	35	.57*
Summer	31.6	19	.68
Fall	59.5	42	1.54*

AOM — acute otitis media, RR — relative effusion-free ratio, OMRC — Otitis Media Research Center, USC — Upper St Clair.

*Significance at $p < .05$.

For those variables classified into more than one category, the relative risks and significance levels presented in Tables 18 and 19 were computed by comparison of each level of the variable to the remainder of patients. In addition, for polychotomous variables, a test for trend was used if the variable was ordered (age and duration); for unordered variables (season), a higher degree of freedom χ^2 statistic was used.

Two hundred twenty such children with the diagnosis of nonsevere acute otitis media were entered initially. At the 2- and 6-week end points, 173 and 127 subjects, respectively, were eligible for the analysis of presence or absence of effusion. Table 18 shows several different characteristics for the 2- and 6-week end points.

At the 2-week end point, age was strongly related to the presence or absence of middle ear effusion. Children younger than 2 years old showed a higher risk of having effusion ($p < .05$), and those 6 to 12 years old had an increased chance of being effusion-free ($p < .01$). Laterality of effusion at entry was also associated with resolution of middle ear effusion. Children who had bilateral effusion at entry were less likely to be effusion-free than those with unilateral effusion ($p < .05$). Also of significance at the

2-week end point was the sex of the child: girls were more likely to be effusion-free than boys ($p < .01$). At the 6-week end point, laterality of effusion at entry remained statistically significant ($p < .01$). Factors such as race, number of prior episodes of acute otitis media, site of study, and season at entry showed no statistical significance at either of the two end points. The presence or absence of the symptoms and signs that were used to characterize acute otitis media was not statistically significant as a predictor of effusion at the 2- and 6-week end points.

In addition to evaluating resolution of middle ear effusion, we also summarized recurrence of acute otitis media by the 6-week visit as an outcome variable (Table 19). Of the different characteristics evaluated, only two, age and season at entry, were statistically significant. Children less than 2 years of age were at a higher risk of having a new episode of acute otitis media by the 6-week end point. The test for trend in proportions for age showed significance ($p = .03$). None of the other factors showed any statistical significance in relation to recurrence of acute otitis media.

A variety of factors have been identified that may be associated with the outcome of acute otitis media. Whether or not a variable is prognostic may depend upon how the outcome is specified and upon the actual time at which the outcome is measured. For example, at the 2-week end

point, significantly more girls than boys were effusion-free. At the 6-week end point, there was no statistically significant difference between the effusion-free rates. Also, whether or not a result is statistically significant depends on the sample size.

The symptoms and signs used to identify acute otitis media as distinct from otitis media with effusion in themselves are not strongly prognostic at the measured end points. Only nonsevere episodes of acute otitis media were included in this report. In an analysis of severe episodes of acute otitis media, such symptoms and signs might be of prognostic value.

Variables that are prognostic for acute otitis media may be different from those for otitis media with effusion. For instance, in children with acute otitis media, age may be a factor in regard to both resolution of middle ear effusion at the 2-week end point and recurrence of acute otitis media. However, Mandel and colleagues (this Supplement, p 29) report that for children with otitis media with effusion, age does not appear to be related to outcome. Thus, it seems important to distinguish otitis media with effusion from acute otitis media when discussing prognostic factors.

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OTITIS MEDIA IN THE FIRST YEAR OF LIFE

COLIN D. MARCHANT, MD; PAUL A. SHURIN, MD

Onset of acute otitis media with effusion in the first year of life carries a high risk of subsequent recurrent acute otitis media.^{62,110} Occurrence of otitis media with effusion for prolonged periods in the first 6 months of life may produce impairment of language acquisition.⁵⁹ Thus early infancy is an important period in terms of both the pathogenesis and consequences of middle ear disease. In this report, we review the findings from two previous investigations of otitis media in early infancy.^{111,112}

COURSE AND OUTCOME OF OTITIS MEDIA IN FIRST YEAR OF LIFE

Aims and Methods. To study the early development of middle ear disease and its clinical manifestations, we performed a prospective study of otitis media in a cohort of infants recruited in the newborn period.¹¹¹ Primary medical care was provided by two nurse practitioners and three pediatricians. Infants were examined at well-child visits at ages 2 weeks and 2, 4, 6, 9, and 12 months, when they sought care for acute illness, and at monthly intervals after diagnosis of otitis media until middle ear effusion resolved. Otitis media was diagnosed by pneumatic otoscopy performed by observers with documented interobserver agreement. Episodes of otitis media were treated with a 14-day course of amoxicillin or other antimicrobial agents according to a standard treatment protocol.

Results and Conclusions. Otitis media occurred in 77% of infants in the first year of life. Twenty-four of 70 (34%) developed otitis media before 2 months of age. The findings in this group with early onset disease were striking.

1. These infants had a 33% chance of developing bilateral otitis media with effusion for 3 months or longer.

2. This risk was eight times that experienced by the remainder of the study population.
3. The early-onset group comprised fully 80% of those who developed prolonged otitis media with effusion.
4. Symptoms such as fever or irritability were absent at the time of presentation in nearly half of the infants.

In addition, 46% of infants with otitis media in the first year of life experienced three or more episodes. We conclude that otitis media in early infancy is often asymptomatic and carries a high risk of chronic otitis media with effusion.

Discussion. These findings demonstrate the high morbidity of early onset of otitis media with effusion and have formed the basis for intervention trials of both chemoprophylaxis and immunoprophylaxis. The finding that the disease often presents at well-child visits without fever or irritability indicates that careful otoscopic evaluation by pneumatic otoscopy or other reliable diagnostic methods is required; otherwise the disease will go undetected in early infancy.

Other prospective studies that included the first year of life^{59,75} demonstrate markedly different rates of otitis media occurring during this period (Table 20^{59,75,111}). Population-based studies of otitis media performed in Sweden⁶² and Finland,⁶⁷ and screening studies using tympanometry in Denmark,⁵¹ suggest lower incidence and prevalence of otitis media in early infancy. These divergent findings may be due to differences in the reliability of diagnostic methods and criteria employed, racial and socioeconomic factors, differences in feeding practices, or the extent of medical treatment. Further studies thus are

TABLE 20. INCIDENCE OF OTITIS MEDIA DURING FIRST YEAR OF LIFE IN PROSPECTIVE STUDIES

Location	Reference	Type of Feeding	Percent With One or More Episodes of Otitis Media by Age	
			6 mo	12 mo
Boston	Teele et al ⁵⁹	Not specified	25	47
Helsinki	Saarinen ⁷⁸	Breast	0	28
		Breast and bottle	2	32
		Bottle	10	53
Cleveland	Marchant et al ¹¹¹	Primarily bottle	71	77

needed to determine the incidence, course, and associated risk factors of otitis media in early infancy.

OBJECTIVE DIAGNOSIS OF OTITIS MEDIA IN EARLY INFANCY

Aims and Methods. To date, the accuracy of objective diagnostic methods has not been demonstrated in early infancy. To fulfill the need for objective diagnosis, we have determined the diagnostic efficacy of tympanometry and ipsilateral acoustic reflexes in infants less than 5 months of age using a Grason Stadler 1723 otoadmittance meter.¹¹² Susceptance tympanometry was performed with a 660-Hz probe tone. Ipsilateral acoustic reflexes were measured with a 660-Hz probe tone and a 1,000-Hz activator. Criteria for middle ear effusion were either a tympanogram peak susceptance of <0 mmho (flat tympanogram), or an ipsilateral acoustic reflex absent or equal to 110 dB hearing level. Pneumatic otoscopy was performed without knowledge of objective findings by experienced observers. Tympanocentesis was performed when clinically indicated in ears with abnormal otoscopic findings.

Results and Conclusions. In 136 ears of 73 subjects, agreement among tympanometry, ipsilateral acoustic reflex thresholds, and pneumatic otoscopy was substantial (Table 21). Tympanocentesis was performed in 39 ears, and middle ear exudate was demonstrated in 36. Peak tympanogram susceptance was <0 mmho in 34 of 36 (sensitivity = 94%). Ipsilateral acoustic reflex findings indicated middle ear effusion in 35 of 36 (sensitivity = 97%).

TABLE 21. AGREEMENT AMONG TYMPANOMETRY, IPSILATERAL ACOUSTIC REFLEX THRESHOLDS, AND PNEUMATIC OTOSCOPY IN 136 EARS OF INFANTS LESS THAN 5 MONTHS OF AGE

	Otoscopy Diagnosis of OME		Peak Tympanogram Susceptance	
	Present	Absent	≤0 mmho	>0 mmho
Ipsilateral acoustic reflex				
Absent or threshold 110 dB HL	62	7	63	6
Threshold ≤100 dB HL	5	62	5	62
Peak tympanogram susceptance				
≤0 mmho	63	5		
>0 mmho	4	64		

Agreement = 91% to 93%; $\kappa = 0.82$ to 0.86 for all three comparisons.
OME — otitis media with effusion.

These findings demonstrate that these procedures using the instrument and diagnostic criteria stated above are accurate in this age group and can be used to further our knowledge of otitis media in early infancy.

Discussion. In future studies of otitis media in the first year of life, consideration must be given to a number of methodologic issues.

1. Since the onset of disease is asymptomatic in almost half of infants, population-based studies using episodes of clinical presentation with illness to define disease incidence may fail to detect significant early episodes. Thus, careful surveillance is required in prospective studies.

2. Documentation of otitis media using objective diagnostic methods will be essential. The diagnostic efficacy of these methods should be evaluated in the age group to be studied.

3. The contribution of multiple risk factors must be assessed for interstudy comparison. Standardized criteria should be used to evaluate risk factors and allow comparisons among these studies.

4. Studies of different populations in various locations will be required to fully determine the incidence, course, and significance of otitis media in early infancy.

AUDIOLOGIC CONSIDERATIONS: BEYOND THE THRESHOLD

ROBERT J. NOZZA, PHD

In most cases of otitis media with effusion, some degree of hearing loss can be measured. The mean hearing threshold level for recognition of speech, for example, is about 25 dB hearing level (HL) in children with otitis media with effusion¹¹³ and constitutes a "mild" hearing loss according to conventional definitions. There is, however, considerable variability in the amount of hearing loss that accompanies otitis media with effusion; therefore, hearing thresholds have not been helpful in either defining or identifying the disease. Hearing sensitivity has been used only as a secondary outcome measure in clinical studies of otitis media with effusion and as an aid to making management decisions. Even in this limited context, elevated hearing thresholds are valuable only to the extent that they tell us something about the accompanying loss of function with respect to relevant auditory tasks.

Historically, one of the greatest challenges faced by audiologists has been the determination of a relationship between audiometric thresholds and the degree of handicap a given person will experience. First, hearing thresholds are a reflection of only the most rudimentary, albeit essential, of auditory tasks — detection. More complex auditory functions, such as discrimination, recognition, selection, and others, are far more important to a listener's ability to function in the environment. The more complex dimensions of hearing certainly are affected by the loudness of a signal; therefore, knowledge of detection thresholds is important. However, the relationships among hearing threshold, the intensity of environmentally significant auditory signals, and ability or need to perform specific complex auditory tasks are not well established even in adults. How these factors interact in infants and young

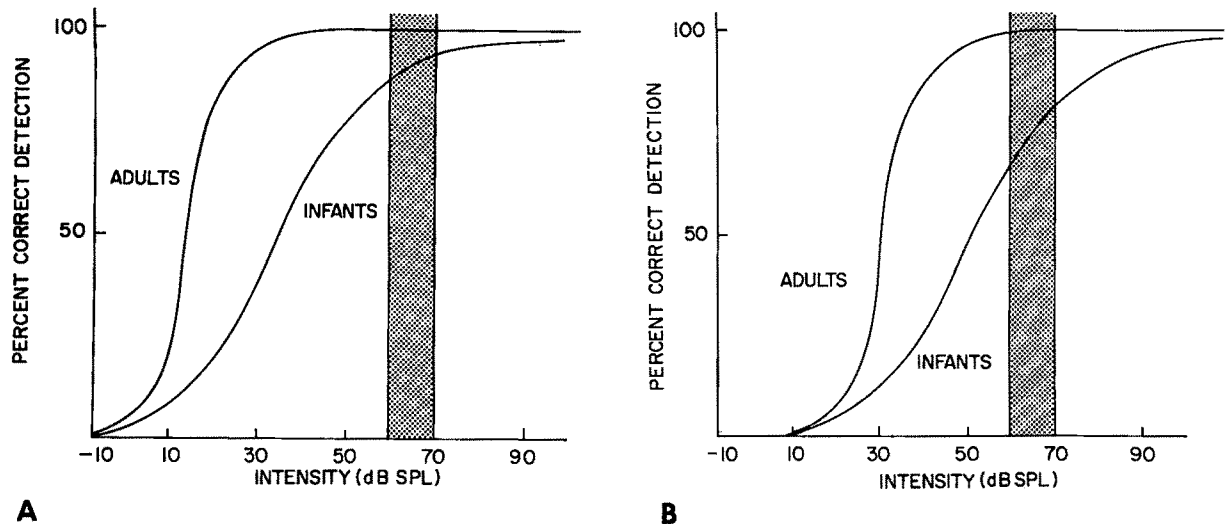


Fig 6. Hypothetical performance-versus-intensity functions for infants and adults for auditory detection task. Shaded bar represents average intensity of conversational speech. A) Speech is sufficient for both infants and adults with normal hearing to achieve near-maximum performance. B) Curves have been shifted by 20 dB, simulating small shift in hearing sensitivity that might accompany otitis media with effusion. Average level of speech still intersects adult curve at maximum performance, but now encounters infant curve at performance levels well below maximum and in region in which small decreases in intensity of speech will cause large decreases in performance.

children during the process of language acquisition is not clear.

Even when we have assumed that we can derive information regarding a child's ability to perform relevant auditory tasks from detection thresholds, it often occurs that there is a difference between the two ears. Because a person with a given hearing loss in the better-hearing ear may be affected differently depending on the degree of hearing loss in the poorer-hearing ear, the use of "better-ear" or "worse-ear" hearing threshold level as an index of overall competence is not always appropriate.

Northern and Downs¹¹⁴ have argued that our definition of auditory impairment should be made more strict for young children than for adults. They note that the requirements for quality auditory input are different for children in the process of acquiring language than for adults or older children with sophisticated language skills. Naremore¹¹⁵ and Menyuk¹¹⁶ have provided informative discussions of the potential effects of hearing loss on the development of language. In recent years, data that are relevant to the points they have raised have begun to appear.

There have been a number of studies done recently in which it has been shown that infants in the first year of life have hearing thresholds for pure tones and for speech that are poorer than those of adults. Pure tone thresholds differ by 5 or 10 dB in high frequencies and by over 20 dB in the low frequencies. Detection threshold for a consonant-vowel syllable such as /ba/ is 15 to 20 dB poorer in infants and 10 dB poorer in preschoolers than in adults. Developmental change in hearing is not a new or controversial finding, but the effect is sometimes obscured by the way we measure and report audiometric results in our clinical studies. For example, the speech recognition threshold (SRT) is often reported as an index of hearing sensitivity. The SRT is the threshold for recognition of selected words presented monaurally under earphones. The kind and number of words used and the response required differ depending on the age or developmental level of the child; therefore, direct comparisons of SRTs across wide age

ranges may be misleading. Further, for infants and very young children, a measure called the speech awareness threshold (SAT) is often reported. This is a threshold for awareness, or detection, of speech sounds in a sound field. While mean SAT estimates often look very similar to mean SRT estimates in clinical studies of otitis media with effusion, comparisons between the two are improper. Sound field hearing sensitivity is better than monaural sensitivity, and the SAT is not measuring each ear separately. We cannot estimate SRT in infants for obvious reasons, but we can estimate SAT in older children and adults. When this is done, the 10- and 20-dB differences mentioned above are revealed.

Studies of discrimination, masking, binaural function, and speech perception have demonstrated that infants and young children have quite sophisticated auditory capabilities. They can do far more with auditory information than simply detect its presence; therefore, we must assume that from very early in life, infants are incorporating auditory information into the task of learning about the world around them.

In addition to the evidence that hearing sensitivity changes with age, there appears to be developmental change in processing of complex auditory information as well. For example, consider performance on word intelligibility tests. While performance improves with increases in loudness of the stimulus words for both children and adults, younger children require greater signal intensity (or signal-to-noise ratio) than older children in order to achieve maximum performance.¹¹⁷ There is also evidence that the rate of increase in performance with increase in the loudness of the signal improves with age as well. A similar effect has been demonstrated with infants in a speech-sound discrimination task. It has been shown that infants can perform optimally in a speech-sound discrimination task when stimuli are presented at 60 and 70 dB SPL, but perform very poorly when stimuli are presented at 50 dB SPL.¹¹⁸

How important are these developmental differences in the requirement for signal intensity when it comes to the

infant's or child's interaction with auditory information in the environment? Dobie and Berlin¹¹⁹ have discussed the impact of a "mild" reduction in hearing sensitivity on ability to process the speech signal. They state that conversational speech is usually about 65 to 70 dB SPL (50 to 55 dB HL) at 1 m from the talker. They also state that a 20-dB reduction can cause the loss of important information in the speech signal. Recall that normal-hearing infants have a 15- to 20-dB disadvantage to begin with, onto which the loss associated with otitis media with effusion is added. The combined effects of poorer sensitivity and an overlay of hearing loss due to otitis media with effusion is schematically pictured in Fig 6. The implication is that the infants and younger children, when performing complex auditory tasks in the environment, are closer to the margin at which a reduction in sensitivity will reduce performance significantly, that is, cause a "handicap."

In summary, infants and younger children with otitis

media with effusion may be operating with hearing sensitivity that is much more handicapping than is suggested by the typical "mild" hearing loss associated with the disease. Given the need for greater signal level in order to perform complex auditory tasks, and the signal intensity levels normally encountered in real-world interactions, it is clear that prelingual infants can be greatly compromised by the threshold shift associated with an effusion in the middle ear. By what mechanism this kind of hearing loss might cause long-term developmental problems is still speculative. However, during the time that a young child has otitis media with effusion, performance of auditory tasks that probably are important to prelinguistic/linguistic competence is surely impaired. Efforts should be made to further our understanding of the effects of reduced sensitivity on the ability of infants and young children to perform auditory tasks that are more closely linked with the development of speech and language.

PREVALENCE AND PROGRESSION OF SEQUELAE FOLLOWING SECRETORY OTITIS

MIRKO TOS, MD; GERD HVID, MD; SVEN-ERIC STANGERUP, MD; ULRİK KOKS ANDREASSEN, MD

INTRODUCTION

This study analyzes different types of eardrum disease that constitute the most important sequelae following secretory otitis. Eardrum changes are the direct cause of hearing impairment occurring after normalization of the tubal function and after the production of middle ear effusion has ceased. Although the hearing impairment caused by minor changes may not be socially disturbing during school age, it may cause a hearing handicap later on when incipient presbycusis sets in. The eardrum changes may progress later on in life, and we have argued previously that all chronic diseases, including cholesteatoma, originate from changes of the tympanic membrane brought about in childhood by secretory otitis and chronic tubal dysfunction.¹²⁰

Another sequela following secretory otitis is reduced pneumatization. Studies of cohorts of otherwise healthy children with secretory otitis have suggested that hypocoelularity is the result rather than the cause of secretory otitis.¹²¹ Other sequelae include mucosal changes such as formation of adhesions, membranes, and cholesterol granulomas and mucosal thickening in the middle ear, as well as histologic changes of the epithelium.¹²²

MATERIAL AND METHODS

Our repetitive tympanometric screenings of three cohorts of otherwise healthy children have always included otoscopy, and in children 5 years of age and older, otomicroscopy also. All changes of Shrapnell's membrane and the pars tensa were recorded, graded, and marked on a drawing of the eardrum. The prevalence of the different types of disease will be analyzed on the basis of cohort III, which originally comprised 373 otherwise healthy children born during the first 10 days of every month in 1975 and living in two municipalities of Copenhagen County, comprising 130,000 inhabitants. The children first were examined by tympanometry in February 1979, when they were 4 years old, and again every 3 months until February 1980. Otomicroscopy first was performed at the fifth trial

in February 1980, when the children were 5 years old, and has been repeated annually until the children were 10 years old, in 1985. This study is based on results obtained at these six annual examinations using otomicroscopy.

ATTIC RETRACTIONS

Definition. We have divided the retractions of Shrapnell's membrane into four types. Type I represents a slight retraction with air between Shrapnell's membrane and the neck of the malleus. Type II indicates a retraction extending to the neck of the malleus, and no air is present. Shrapnell's membrane may be adherent to the neck of the malleus, but this is not always the case. Type III indicates a retraction extending beyond the bony annulus, but on tilting the head of the patient, air can be seen in the attic. There may be some resorption of the bony annulus, whereas the area of Shrapnell's membrane is enlarged. In type IV retraction, there is pronounced bone resorption, and Shrapnell's membrane is adherent to the heads of the malleus and the incus, which are clearly visible. Because of bone resorption, the bottom of the retraction is still visible. When the bottom of the retraction cannot be seen even after the pocket is cleansed, the condition is denoted as attic cholesteatoma.

Prevalence. In children 5 years of age, attic retractions occurred in 18% of the ears (Table 22), and the prevalence increased significantly up to the age of 7 (χ^2 test, $p < .001$). In children between 7 and 8 years of age, the prevalence of slight attic retractions decreased, and up to the age of 10 it remained almost constant. Retractions of types III and IV occurred only in a few ears in this series.

Stability and Progression. Type I and in some instances type II retractions are completely reversible and therefore are unstable conditions that change from trial to trial. This is the explanation of the decrease in the prevalence of type I and II retractions from age 7 to age 8 (Table 22), as these types of disease show a pronounced tendency to recover following normalization of middle ear pressure.

TABLE 22. PREVALENCE OF EARDRUM DISEASE AT VARIOUS AGES IN COHORT OF HEALTHY CHILDREN

Type of Attic Retraction	Age, No. of Ears, % of Ears					
	5 444 (%)	6 444 (%)	7 444 (%)	8 414 (%)	9 406 (%)	10 470 (%)
I	9.2	14.9	11.5	9.2	11.1	10.6
II	7.0	9.2	13.7	8.5	9.6	11.1
III	1.1	2.3	3.4	5.8	4.4	4.3
IV	0.7	1.3	0.9	0.5	0.3	0.4
Total	18.0	27.7	29.5	24.0	25.4	26.4
χ^2 test	p < .001			NS		
Attic only*	14.9	19.8	21.6	15.2	14.5	14.7
Attic and tensa*	3.1	7.9	7.9	8.7	10.8	11.7
Tensa only*	5.7	9.2	9.2	6.5	7.4	6.4
Total disease	23.7	36.9	38.7	30.4	32.7	32.8
χ^2 test	p < .001		p < .01			

*Prevalence of attic retractions only, retractions of attic and disease of pars tensa, and disease of pars tensa only.

Type III and IV retractions are more stable conditions, some of which may progress into attic cholesteatoma. If the self-cleaning ability of the retraction is disturbed, crust formation and infection may lead to proliferation of the epithelium, and eventually the condition may deteriorate into attic cholesteatoma.

COMBINED DRUM DISEASE

Either attic retractions occurred alone (Table 22) or in combination with changes of the pars tensa, or tensa retractions occurred alone without attic retractions. The total prevalence of eardrum changes, as well as the prevalence of the different types of disease, is shown in Table 22. In children from 5 to 6 years of age, the prevalence of eardrum changes increased significantly; this applied both to attic retractions and pars tensa changes. In children from 7 to 8 years of age, the prevalence of eardrum changes decreased significantly, especially the solitary attic retractions and the slight changes (Table 22). In healthy children after the age of 8, one third of the eardrums display some kind of disease.

PARS TENSA DISEASE

The combination of three basal changes — atrophy, tympanosclerosis, and retraction — results in different manifestations that must be defined thoroughly in order to determine their prevalence and possible progression.

Definition and Progression. Atrophy denotes an eardrum that is thinner than normal. The atrophy may be localized in certain segments of the eardrum, or it may be diffuse and involve the whole membrane. The eardrum may have near-normal mobility and elasticity, or it may be flaccid. The ability to recover completely is reduced in an atrophic eardrum with a perforation resulting from a commonplace episode of acute suppurative otitis. There is also an increased risk of a permanent perforation. Furthermore, a negative middle ear pressure will result more often in retraction than is the case with a normal eardrum. In severe cases of diffuse atrophy with retraction, the atrophic eardrum is slack and "too big," having lost its elasticity. The middle ear has become more or less atelectatic. This condition is serious and may lead to tensa retraction cholesteatoma, because on further retraction medial to the malleus fold, the annulus, and the malleus handle, the eardrum covers all the walls of the tympanic cavity, including the tympanic orifice or eustachian tube. When

TABLE 23. PREVALENCE OF ABNORMALITIES OF PARS TENSA AT VARIOUS AGES IN COHORT OF HEALTHY CHILDREN

Pars Tensa Abnormalities	Age, No. of Ears, % of Ears					
	5 444 (%)	6 444 (%)	7 444 (%)	8 414 (%)	9 406 (%)	10 470 (%)
Atrophy	2.5	7.0	6.3	6.3	6.2	8.1
Atrophy with fixation	0.7	2.3	2.0	1.7	3.2	2.3
Adhesive otitis	—	—	—	0.2		
Atrophy with perforation	0.2	0.2	0.2	±	0.2	0.2
Atrophy with tympanosclerosis	0.7	2.0	1.4	1.2	2.7	2.3
Tympanosclerosis only	4.7	5.6	7.2	5.8	5.9	5.1
Total, abnormal pars tensa	8.8	17.1	17.1	15.2	18.2	18.0
χ^2 test	p < .001					

The one patient with perforation did not attend this evaluation.

its self-cleaning ability is compromised, the retraction may become infected and advance up toward the attic.

The term atrophy with fixation denotes an eardrum that is flaccid and thin posteriorly and in contact with the long process of the incus, a condition known as myringoincudopexy. On continued resorption, the retraction develops into a myringostapediopexy. This condition may deteriorate further into adhesive otitis, sinus cholesteatoma, or tensa retraction cholesteatoma.

The term adhesive otitis indicates that the retracted eardrum is adherent to the medial wall of the tympanic cavity. Usually, there is also myringostapediopexy. If the self-cleaning ability of the retraction is disturbed, the condition may progress to sinus cholesteatoma or tensa retraction cholesteatoma.

Atrophy and tympanosclerosis is a frequent combination, eg, with atrophy inferiorly and tympanosclerotic plaques posteriorly or anteriorly. Later, in connection with acute otitis, a permanent perforation may arise in the atrophic part of the eardrum.

Prevalence and Stability of Tensa Changes. In children 5 years of age, 9% of the ears showed changes of the pars tensa (Table 23). In children 6 years of age, the prevalence had increased significantly, to 17%. After this age, the prevalence remained constant.

The prevalence of severe changes, especially atrophy with fixation, cannot be disregarded completely, in view of the fact that this is a randomized cohort of healthy children. Several of the eardrum changes may in adulthood progress to adhesive otitis or sinus or tensa cholesteatoma, and perforations may arise as a result of imperfect healing of a perforation in an atrophic area, possibly caused by a commonplace episode of acute otitis.

The slightest of the eardrum changes are not very stable, and a small tympanosclerotic plaque may have disappeared at the next trial.¹²² Tympanosclerosis has been shown to be a dynamic process composed of calcification and decalcification.¹²³ Also, in cases of very slight changes, there may be some intraindividual and interindividual variations in the evaluations of the pathologic features. Slight atrophy or tympanosclerosis may be recorded by the

same investigator as normal at one trial and as slightly pathologic at the next. With increasing numbers of trials, there is, of course, an even greater risk of misinterpretation of the very slight changes.

The results of our prevalence studies reported here are derived from cohort III, in which the tympanometric conditions were poorer than in cohorts I and II. Since the literature contains no other systematic studies of the preva-

lence of eardrum changes, there is good reason to study cohorts. The incidence of eardrum changes in a clinical series of children treated for secretory otitis is considered higher than that demonstrated herein. At follow-up 3 to 8 years and 10 to 16 years after treatment with ventilation tubes and adenoidectomy, we found eardrum changes in 55% and 58% of the ears, respectively; adhesive otitis accounts for 2.5% and atrophy with fixation for 4% of the changes.

INCIDENCE AND PREVALENCE OF COMPLICATIONS OF OTITIS MEDIA

MARGARET A. KENNA, MD

Otitis media in both the acute and chronic forms is a common disease process, most prominent in the pediatric population. The various forms include acute otitis media, otitis media with effusion, and chronic suppurative otitis media with and without cholesteatoma. The incidence and prevalence of acute otitis media and otitis media with effusion, especially after a child is over 1 year of age, has been established fairly well by several recent studies.^{59,105} The incidence and prevalence of chronic suppurative otitis media is not well established, although it is known to be very common in certain subpopulations such as patients with cleft palate and in Alaskan Eskimos and American Indians.¹²⁴

No epidemiologic study, however, has addressed the true incidence and prevalence of the complications of otitis media using all patients with otitis media as the denominator. The complications and sequelae can be divided into intratemporal and intracranial forms (Table 24).

The available literature does document the marked decrease in complications since the advent of antimicrobial usage. Kafka¹²⁵ studied 2,100 patients with acute otitis media and 1,125 with chronic mastoiditis. Of the total 3,225 patients, 209 (6.5%) had complications. Forty-eight percent had meningitis, 27.5% had lateral sinus thrombosis, 16.5% had brain abscess, and 13% had other complications. The mortality was a striking 76.4%. This high mortality secondary to otitis media was confirmed by Rosenwasser and Adelman,¹²⁶ who noted that in the 5 years immediately preceding the introduction of sulfa drugs (1928 to 1933), 1 in 40 deaths at the Los Angeles County Hospital resulted from an intracranial complication of otitis media.

Fortunately, all this changed with the introduction of the sulfonamides in the 1930s, followed by penicillin in the 1940s. Gower and McGuirt¹²⁷ evaluated 334,884 admissions to the North Carolina Baptist Hospital from 1963 to 1982. One hundred of these patients had central nervous system complications of otitis media: 76% had meningitis, 6% had brain abscess, 5% had subdural effusions, 5% had lateral sinus thrombosis, 5% had otitic hydrocephalus, and 3% had subdural empyema. The mortality was 10%. This precipitous drop in mortality also was noted by Lund,¹²⁸ who found a decrease in mortality from intracranial complications of otitis media from 36% in 1939 and 1949 to 0% in 1961 to 1971. Courville¹²⁹ found that the death rate in 1944 to 1953 was 10% of the rate in 1929 to 1933. Sorensen¹³⁰ found that not only had the mortality from complications decreased by 86%, but the mastoidectomy rate had fallen from 20% in 1938 to 2.5% in 1948.

Clearly, then, the overall rate of intracranial complications and the mortality from these complications have decreased dramatically since the introduction of antimicrobials. Although it seems reasonable to assume that the intratemporal complication rate has also decreased, there is less documentation. Petrositis, which often leads to meningitis, extradural abscess, and labyrinthitis, has decreased secondary to antimicrobial therapy.¹³¹ Facial nerve paralysis was evaluated by May.¹³² He noted 70 cases (between 1962 and 1983) of facial nerve dysfunction secondary to infectious causes, 52 of which were from otitis media (36 of acute otitis media and 16 of chronic otitis media).

The incidence of cholesteatoma has been looked at in a study by Harker.¹³³ From Sept 1, 1975, to Feb 29, 1976, 86 surgically verified cholesteatomas were identified in Iowa. This gave an incidence of 6 in 100,000 population, with the peak during the second and third decades of life. There was no mention of whether otitis media had preceded the cholesteatomas or whether some of them could have been congenital. In addition, the population of Iowa is primarily white and middle class; therefore, this incidence may not be applicable to other populations.

During 1977, also, the incidence of cholesteatoma in cleft palate patients in Iowa was reported to be 7.1%.¹³⁴

TABLE 24. SUPPURATIVE COMPLICATIONS AND SEQUELAE OF OTITIS MEDIA

Intratemporal
Hearing loss
Perforation
Chronic suppurative otitis media
Cholesteatoma
Retraction pocket
Adhesive otitis media
Tympanosclerosis
Ossicular discontinuity and fixation
Mastoiditis
Petrositis
Labyrinthitis
Facial paralysis
Cholesterol granuloma
Infectious eczematoid dermatitis
Intracranial
Meningitis
Subdural empyema
Focal otitis encephalitis
Brain abscess
Lateral sinus thrombosis
Otitic hydrocephalus

All of these patients were noted to have preexisting otitis media with effusion. This rate, however, cannot be applied to patients without cleft palate.

As for the other intratemporal complications, there are minimal data available on hearing loss in acute otitis media and otitis media with effusion. Fria et al,¹³⁵ who evaluated 553 children with otitis media with effusion, found 65.8% with pure tone averages poorer than 20 dB; 51.8% had pure tone averages poorer than 25 dB, and in 38.7%, pure tone averages were worse than 30 dB. It is assumed that patients with acute otitis media also have some element of hearing loss during their acute episode and until the effusion clears; however, this has never been studied adequately.

Complications of otitis media still occur, although much less commonly than in the preantibiotic era. In parts of the world in which medical care is not as advanced or available, devastating complications still are recognized with some frequency.¹³⁶

Determination of the actual incidence and prevalence

of complications secondary to otitis media would require a large number of patients with documented otitis media to be followed at frequent intervals over many years. Tympanometry and audiometry would need to be performed routinely. Patients undergoing surgical procedures, including tympanostomy tube insertion, would need to be monitored carefully for any preoperative and postoperative complications and sequelae.

Various population subgroups would need to be considered, as the complication rate and the prevalence and incidence rate might differ. Counting patients with the "major" complications, such as meningitis and brain abscess, is not adequate. All patients with otitis media, whether acute otitis media, otitis media with effusion, and/or chronic suppurative otitis media, would have to be observed for the subtler findings of hearing loss, perforation, and tympanosclerosis. Although this sort of cohort study would be a major undertaking, it would help establish the actual number, type, and importance of complications and sequelae, and would reinforce why the treatment of early otitis media is so essential.

EPIDEMIOLOGY OF ETIOLOGIC FACTORS

Microbiology

EPIDEMIOLOGY OF THE MICROBIOLOGY OF ACUTE OTITIS MEDIA

ELLEN R. WALD, MD

There has been continued interest in the microbiology of acute otitis media over the last decade. In addition to observation and documentation of changes in the bacterial agents that cause acute otitis media, substantial interest has been generated in the nonbacterial causes that result in "sterile" middle ear effusions.

To update the Pittsburgh report on the epidemiology of the microbiology of acute otitis media, the bacterial isolates from three ongoing studies and one recently completed comparative study of antibiotic efficacy were reviewed.¹³⁷ The criteria for entry into these studies included fever, otalgia or irritability, and otoscopic findings of an opaque tympanic membrane with impaired mobility. Sterilization of the external ear canal was accomplished with a 70% alcohol solution that was allowed to remain in the canal for 1 minute and then was aspirated through the speculum of the operating head of the otoscope. The data for 208 children or 416 ears have been combined.

The bacterial agents in their relative order of prevalence are shown in Table 25. Both *Hemophilus influenzae* and *Branhamella catarrhalis* may be β -lactamase-producing and thereby ampicillin-resistant. In this series, 6 of 22 (27%) of the *H influenzae* and 12 of 14 (86%) of the *B catarrhalis* strains were β -lactamase-positive. During the past 6 years that the OMRC has tabulated data, the prevalence of β -lactamase-producing *H influenzae* in the acute otitis media treatment studies has varied between 17% and 36%. A high prevalence of β -lactamase-producing *B catarrhalis* was first noted in 1981; this rate has varied, but has remained above 67% and in 1986 was 82% (Table 26).

In every series of patients with acute otitis media, a significant number, otoscopically and clinically indistinguishable from the rest, are found to have sterile middle ear effusions. Candidate etiologic agents in these cases are viruses, *Mycoplasma*, *Chlamydia*, *Legionella*, and anaerobes of the upper respiratory tract. The history of the role of respiratory viruses has been the most interesting. Early attempts to isolate viruses and *Mycoplasma* from middle ear fluid were largely unsuccessful. Klein and Teele¹³⁸ summarized these studies in 1976, noting the infrequent documentation of virus recovery from middle ear fluid. The conclusion drawn was that viruses were probably not important in the causation of acute middle ear disease, but

might be important in the epidemiology of the disorder, ie, these agents cause simple upper respiratory tract infection and by so doing result in eustachian tube dysfunction. The eustachian tube dysfunction in turn predisposes to secondary bacterial infection of the middle ear cleft.

The role of viruses in acute otitis media has recently been evaluated with new techniques of antigen detection and state-of-the-art tissue culture techniques for virus identification.¹³⁹⁻¹⁴² It is now apparent that viruses are important both etiologically and epidemiologically in acute otitis media. The viruses that have been identified in the middle ear and nasopharynx of patients with acute otitis media include respiratory syncytial virus, influenza virus, enterovirus, rhinovirus, parainfluenza, and adenovirus. These viruses are recovered from approximately 20% of patients.^{138,141,142} In some cases, viruses are the only isolate from the middle ear effusion. In other instances, viruses and bacteria are recovered together, suggesting an important role of viral-bacterial interaction. The highest yield for the recovery of viral agents was in patients who had been ill for only a few days.

The role of *Chlamydia trachomatis* as a cause of middle ear effusion also has been explored recently. This microbiologic species is known to cause conjunctivitis and pneumonitis in early infancy. The bulk of available data suggest a very minimal role for this organism in both upper and lower respiratory tract disease in children over 6 months of age.^{143,144}

In a recent review of illnesses in infants born to women with *C trachomatis*, incidence rates for first episodes of otitis were similar to that of a group without exposure to *C trachomatis*, although the exposed group had an earlier onset of infection and were more likely to have recurrences.¹⁴⁵ These associations were not striking, and this study, which identified *Chlamydia*-positive women with a single culture performed between 20 and 36 weeks' gestation, was faulty in many respects.

In the United States, Hammerschlag et al¹⁴⁶ did not recover *C trachomatis* from any of 68 children with chronic otitis media, and Chang et al¹⁴⁷ found it in the middle ear fluid of only 1 of 14 children with persistent otitis media and 2 of 12 children with acute otitis media in 1982. Al-

TABLE 25. BACTERIOLOGY OF ACUTE OTITIS MEDIA, PITTSBURGH 1985-1986

Bacterial Species	No. of Strains	Percent
<i>Streptococcus pneumoniae</i>		36
<i>Hemophilus influenzae</i>		
β -lactamase-positive	6	
β -lactamase-negative	16	22
<i>Branhamella catarrhalis</i>		
β -lactamase-positive	12	
β -lactamase-negative	2	14
<i>Streptococcus pyogenes</i>		4

TABLE 26. PREVALENCE OF β -LACTAMASE-PRODUCING *HEMOPHILUS INFLUENZAE* AND *BRANHAMELLA CATARRHALIS* IN EFFUSIONS FROM ACUTE OTITIS MEDIA

Year	<i>H influenzae</i> (%)	<i>B catarrhalis</i> (%)
1980	25	—
1981	17	67
1982	21	80
1983	22	79
1984	36	68
1985	28	87
1986	34	82

though no more recent data obtained by tympanocentesis are available, it is unlikely that chlamydial isolates account for a major portion of cases of otitis media.

We recently evaluated the role of *Legionella* species in the causation of otitis media with effusion. The increasing prevalence of antibody to *Legionella* with increasing age in the pediatric population suggested an exposure in the form of mild respiratory tract disease in the early years of life.¹⁴⁸ Middle ear effusions were plated on selective media (differential glycine-vancomycin-polymyxin B) and non-selective media (buffered charcoal yeast extract) for 1 week at 35°C. When a sufficient volume of middle ear fluid was available, two tenfold dilutions were prepared and plated similarly. No *Legionella* was identified among 31

samples of middle ear effusion from patients with acute otitis media or from 76 patients with persistent middle ear effusion.

In summary, the bacteriology of acute otitis media has been relatively stable in Pittsburgh over the last few years, with a variable prevalence of β -lactamase-producing *H influenzae* and a consistently high prevalence of β -lactamase-producing *B catarrhalis*. Recent studies have shown an important etiologic role for respiratory viruses and enteroviruses in acute middle ear effusions. *Chlamydia* is of uncertain, but probably limited, importance in middle ear disease; *Legionella* sp were never isolated from 104 middle ear aspirates obtained from acute and chronic effusions.

EMERGENCE OF *BRANHAMELLA CATARRHALIS* AS A MAJOR CAUSE OF ACUTE OTITIS MEDIA IN DALLAS, TEXAS

JOHN D. NELSON, MD

Since 1973 four studies of acute otitis media with effusion have been carried out at Children's Medical Center in Dallas, Texas. Results of the first three studies have been published.¹⁴⁹⁻¹⁵¹ The fourth study is currently under way, and at the time of this analysis, tympanocentesis has been done in 158 ears of 120 children. [A completed study has been subsequently published.¹⁵²]

The patient population has not changed demographically in a significant way during the 13-year period, and the methods for obtaining middle ear fluid, performing cultures, and identifying microorganisms have been essentially the same. Therefore, any changes in the frequency of the various pathogens occurring over time cannot be accounted for by patient selection or methodology.

Pneumococci and *Hemophilus* sp were the predominant pathogens in all four studies (Table 27). Group A streptococci were uncommon in the earlier studies, but were found in 7% of cases in the current study. There was a striking increase in the frequency of *Branhamella catarrhalis*, from 1% to 3% of cases in the earlier studies to 25% in the current study, including 18% in which it was isolated as the sole pathogen.

Altogether, pneumococci were found in 34% of the 120 cases, *Hemophilus influenzae* in 28%, and *B catarrhalis* in 25%. Of the 158 ear cultures performed, 35% grew pneumococci; 28%, *H influenzae*; and 24%, *B catarrhalis*. The organisms were in pure culture in essentially the same proportion with each of the three pathogens: pneumococci, 66%; *Hemophilus*, 70%; and *Branhamella*, 74%.

Hemophilus parainfluenza was identified in five cases in the first study and in four cases in the second study. However, in the two more recent studies, all *Hemophilus* isolates have been speciated as *H influenzae*. Nineteen (9.5%) of the 200 *Hemophilus* strains were type b.

During the current study, cultures of ear drainage were obtained from 31 additional patients after spontaneous rupture of the eardrum within the preceding 24 hours. The organisms isolated and number of cases were as follows: *Staphylococcus aureus*, 9; coagulase-negative staphylococci, 4; *H influenzae*, 4; *Streptococcus pneumoniae*, 4; *Pseudomonas aeruginosa*, 3; *Streptococcus pyogenes*, 2;

viridans streptococci, 2; *B catarrhalis* and *H influenzae*, 2; and *Enterobacter aerogenes*, 1. In three of the four patients whose drainage yielded only coagulase-negative staphylococci, ears with intact membranes were tapped; the culture of the middle ear fluid had *S pneumoniae* in two cases, and that organism plus *Branhamella* and *Hemophilus* in the third case. It seems likely that the history of acute onset of ear disease and rupture was incorrect in the patients with *S aureus* and gram-negative bacilli (other than *Hemophilus*).

β -Lactamase production by bacterial strains was tested by the iodine-starch-penicillin method in the first two studies and by the chromogenic cephalosporinase method in the latter two studies. Only one strain of β -lactamase-producing *Hemophilus* was found in each of the first two studies. In the third study 7 (12%) of 59 *Hemophilus* strains and 9 (75%) of 12 *Branhamella* strains were β -lactamase-positive.

In the current study, β -lactamase production was detected in 6 (13%) of 45 nontypeable *Hemophilus* strains, in 1 (17%) of 6 *H influenzae* type b strains, and in 36 (88%) *B catarrhalis* isolates.

TABLE 27. PATHOGENS ISOLATED IN FOUR STUDIES OF OTITIS MEDIA WITH EFFUSION IN DALLAS

Pathogens	Study 1 5/73- 1/75 (N = 383)	Study 2 11/76- 1/78 (N = 95)	Study 3 2/82- 6/83 (N = 150)	Study 4 10/85- 8/86 (N = 120)
Pneumococci	31.0	22.0	34.0	23.0
<i>Hemophilus</i>	22.0	20.0	17.0	18.0
Type b	1.3	3.2	4.0	4.2
<i>Branhamella</i>	2.0	1.0	3.0	18.0
Pneumococci and <i>Hemophilus</i>	5.0	2.0	5.0	5.0
Pneumococci and <i>Branhamella</i>	0	0	< 1.0	3.0
Pneumococci, <i>Branhamella</i> , and <i>Hemophilus</i>	0	0	0	4.0
Group A <i>Streptococcus</i>	3.0	0	0	7.0

Column numbers indicate percent of patients.

TABLE 28. PATIENTS WITH β -LACTAMASE-PRODUCING BACTERIA

Time	Total No.	No. Positive	% Positive
5/73-1/75	383	1	< 1
11/76-1/78	95	1	1
2/82-6/83	150	7	5
10/85-8/86	120	32	27

Staphylococcus aureus is excluded.

Because patients in the current study were treated with cefaclor, the in vitro susceptibilities of pathogens to that drug were measured. Mueller Hinton broth medium (with added supplement C for *Hemophilus*) was used, and the bacterial inoculum was between 10^4 and 10^5 colony-forming units. The minimal inhibitory concentration (MIC) was determined visually after overnight incubation. The minimal bactericidal concentration (MBC) was determined by quantitative subculture from all clear tubes to agar plates to find the least concentration of antibiotic causing >99.9% killing of the original inoculum.

The median MICs (range) in micrograms per milliliter were as follows: pneumococci, 0.5 (0.25 to 2); β -lactamase-negative *Hemophilus*, 1 (0.12 to 4); β -lactamase-positive *Hemophilus*, 1 (0.5 to 2); β -lactamase-negative *Branhamella*, 0.25 (<0.01 to 0.25); and β -lactamase-positive *Branhamella*, 2 (0.5 to 2).

The median MBCs (range) were as follows: pneumococci, 1 (0.5 to 2); β -lactamase-negative *Hemophilus*, 2 (0.25 to 8); β -lactamase-positive *Hemophilus*, 1 (1 to 4); β -lactamase-negative *Branhamella*, 0.25 (0.06 to 0.25); and β -lactamase-positive *Branhamella*, 2 (1 to 8). Shurin et al¹⁵³ reported a geometric mean MIC of cefaclor for β -lactamase-positive *Branhamella* of 1.35 μ g/mL, with a range of 0.18 to 6.25 μ g/mL for the 20 strains tested.

Cefaclor does not exhibit full stability to the β -lactamase produced by *Branhamella* strains, as evidenced by the eightfold greater MBC of positive strains compared with negative strains. However, the absolute amounts required for inhibition and killing are comparable to those

required for *Hemophilus* and pneumococci.

The emergence of *B catarrhalis* in Dallas as a pathogen of acute otitis media with a frequency rivaling that of *Hemophilus* is similar to the experiences in Cleveland¹⁵⁴ and Pittsburgh,¹⁵⁵ but lags behind those cities by a few years. Between October 1980 and February 1982, Shurin et al¹⁵⁴ in Cleveland found that 26.5% of children had *B catarrhalis* cultured from middle ear fluid, and between October 1981 and March 1982 Kovatch et al¹⁵⁵ in Pittsburgh isolated *B catarrhalis* from 19% of middle ear fluid cultures. However, in the period February 1982 to June 1983 in Dallas we found *Branhamella* in only 3% of cases. The increased frequency of *Branhamella* in middle ear disease occurred sometime between June 1983 and October 1985. The cause for this change is not apparent. The same research microbiologist processed all the cultures in the 1982 and 1983 and the current studies, and the methodology was identical. The investigators in Cleveland and Pittsburgh also could not uncover a ready explanation for the phenomenon. It is conceivable that the pervasive use of amoxicillin during the 1970s and early 1980s has encouraged selection of β -lactamase-producing bacteria as colonizers of the nasopharynx. Alternatively, *B catarrhalis* may have undergone changes and developed virulence factors for respiratory tract epithelium.

As a result of the emergence of *B catarrhalis* as a major pathogen and because the majority of strains produce β -lactamase, more than one fourth of the children studied in Dallas recently have β -lactamase-producing *Branhamella* or *Hemophilus* or both as causes of acute otitis media (Table 28). Amoxicillin has long been the most widely used drug for therapy of this common condition. It appears that cefaclor, Augmentin (amoxicillin and clavulanate potassium) or Pediazole (erythromycin and sulfisoxazole) would be more appropriate, since they are active against β -lactamase-producing bacteria. Trimethoprim-sulfamethoxazole is also active against those strains, but has the disadvantage of being ineffective for group A streptococcal infection.

FREQUENCY OF BACTERIA ISOLATED FROM MIDDLE EAR EFFUSIONS OF CHILDREN FROM THE UNITED STATES, FINLAND, JAPAN, AND DENMARK

CHARLES D. BLUESTONE, MD; KAJ LUNDGREN, MD; MIRKO TOS, MD; TETSUO TAKAHARA, MD

The Workshop conferees from the United States, Finland, Japan, and Denmark presented the frequency with which different bacterial isolates have been cultured from children with acute otitis media and chronic otitis media with effusion in their respective countries. As shown in Table 29,⁵⁵ *Streptococcus pneumoniae* was the most common bacterial isolate and *Hemophilus influenzae* the second most common from middle ears of children with acute otitis media in the United States (D. Rohn, E. R. Wald, unpublished data, 1980-1985), Finland (P. Karma et al, unpublished data, 1986), Japan (T. Takahara et al, unpublished data, 1986), and Denmark.¹⁵⁶ In the United States and Finland, *Branhamella catarrhalis* was the third most frequently isolated pathogen, but in Japan, *Streptococcus pyogenes* and *Staphylococcus aureus* were isolated more often than *B catarrhalis*. Danish children had *H influenzae* as their most common middle ear pathogen in 1973.¹⁵⁶

Table 30 shows that in the United States, Finland, and Japan, *H influenzae* is the most common bacterium isolated from children who have chronic otitis media with effusion and that *S pneumoniae* and *B catarrhalis* are identified less frequently. These and other bacteria can be cultured from approximately one third or two thirds of chronic middle ear effusions.

The rates of β -lactamase-producing bacterial strains obtained from middle ear effusions were reported from the United States and Finland. In the United States, approximately one third of strains of *H influenzae* produced β -lactamase in 1986, whereas in Finland the rate was 16% in 1985. β -Lactamase-producing strains of *B catarrhalis* from the United States and Finland were 86% and 52%, respectively. Even though results of middle ear aspirates are not available from Finland, the frequency of β -lactamase-producing *H influenzae* cultured from the naso-

TABLE 29. PERCENT OF BACTERIA FROM MIDDLE EAR ASPIRATES FROM CHILDREN WITH ACUTE OTITIS MEDIA FROM UNITED STATES, FINLAND, DENMARK, AND JAPAN

	United States* (N = 1,432 Ears) 1980-1985	Finland† (N = 707 Ears) 1977-1978	Japan§ (N = 1,227 Ears) 1984-1986	Denmark ^{ss} (N = 147 Ears) 1973
<i>Streptococcus pneumoniae</i>	29.8	33.8	45.9	19.1
<i>Hemophilus influenzae</i>	20.9	8.5	33.4	27.6
<i>Branhamella catarrhalis</i>	11.7	7.2	2.3	—
<i>Streptococcus pyogenes</i>	3.1	2.1	6.3	8.2
<i>Staphylococcus aureus</i>	1.6	5.0	5.0	17.1
<i>Staphylococcus epidermidis</i>	—	11.5	—	—
"Other"	19.1	3.0	3.9	—
No growth	19.6	39.3	7.2	—

*From D. Rohn and E. R. Wald, unpublished data, 1980-1985.

†From P. Karma et al, unpublished data, 1986.

§From T. Takahara et al, unpublished data, 1986.

TABLE 30. PERCENT OF BACTERIA FROM MIDDLE EAR EFFUSIONS FROM CHILDREN WITH CHRONIC OTITIS MEDIA WITH EFFUSION FROM UNITED STATES, FINLAND, AND JAPAN

	United States (N = 4,483 Ears) 1980-1985	Finland (N = 510 Ears) 1978-1984	Japan (N = 441 Ears) 1984
<i>Hemophilus influenzae</i>	14.7	8.0	20.2
<i>Streptococcus pneumoniae</i>	7.0	4.3	10.6
<i>Branhamella catarrhalis</i>	8.5	3.5	2.3
<i>Streptococcus pyogenes</i>	0.8	0.2	0.9
<i>Staphylococcus epidermidis</i>	—	7.5	—
"Other"	35.3	5.3	4.8
No growth	34.0	66.3	56.0

pharynx was reported to be only 3% in 1985, but 45% of *B. catarrhalis* strains were β -lactamase-positive during the same year.

In summary, the frequencies of the types of bacteria that cause acute otitis media and chronic otitis media with effusion are relatively consistent in the United States, Europe, and Japan. In addition, β -lactamase-producing organisms have been isolated from the United States, Finland, and Sweden.

Allergy-Immunology

ALLERGIC RHINITIS AND ITS POTENTIAL RELATION TO OTITIS MEDIA

PHILIP FIREMAN, MD

The role of allergy in the pathogenesis of otitis media with effusion has been debated for more than 30 years. The potential for allergy to contribute to otitis media with effusion has been suggested by studies reporting higher prevalences of otitis media with effusion in allergic patients and the presence of immune response components in the effusion.¹⁵⁷ However, this hypothesis has been criticized, since these studies lacked appropriate experimental design, had inadequate controls, were retrospective, and did not document the pathophysiology whereby allergy produced otitis media with effusion.¹⁵⁸ Studies of the epidemiology of nasal allergy have been hampered by the lack of completely satisfactory objective methods to define allergic rhinitis. Therefore, this disease has been diagnosed in terms of symptoms, signs, and assumed causation. The diagnosis of allergic rhinitis requires symptoms of sneezing, pruritus, and rhinorrhea associated with immune responses, ie, positive allergy test results, to specific aeroallergens present in the environment during symptomatic periods. These immune responses are usually, but not exclusively, IgE-mediated and can involve immediate and/or late-phase hypersensitivity. Allergic rhinitis can be seasonal (episodic) and/or perennial (year-round). Pollen allergy in temperate climates is typically seasonal, whereas in subtropical and tropical climates pollen allergy can be perennial. Even in the temperate zone, a seasonal increase in symptoms during the winter months can be due to increased exposure to indoor house dust, house dust mite, or storage mold allergens. When symptoms are perennial, it

may indicate that the patient has sensitivity to a number of allergens such as pollens, molds, dusts, and animal products.

By means of questionnaires and symptom diaries, epidemiologic studies have shown a cumulative prevalence of seasonal allergic rhinitis (hay fever) of 10.2% for all ages, with 1.4% for children less than 4 years of age; 4.7% for children 5 to 9 years of age; 9.2% for children and adolescents 10 to 15 years of age; and 16.3% for adolescents and adults 16 to 25 years of age.¹⁵⁹ Thus, the peak incidence of seasonal allergic rhinitis in adolescents and young adults occurs years after the peak incidence of otitis media with effusion in young children. There are no adequate studies of the epidemiology of perennial allergic rhinitis during the winter and spring seasons, when otitis media has its peak incidence. In a series of patients with otitis media with effusion studied for an antihistamine-decongestant drug trial (Decongestant-Antihistamine Study), 5.5% of patients had a history of allergic rhinitis without laboratory testing.¹⁰⁸ Another study of selected children with recurrent and chronic otitis media with effusion who were candidates for replacement of tympanostomy tubes had an incidence of respiratory allergy (seasonal and perennial) documented by history and skin tests of greater than 50%.¹⁶⁰ Thus, many of the patients with chronic otitis media with effusion may well be allergic, but there is a need for more substantive epidemiologic data that correlate nasal allergy with the presence or pathogenesis of

otitis media with effusion.

The contribution of allergy to the pathogenesis of otitis media with effusion may involve several potential mechanisms: 1) the middle ear mucosa responding functionally as a sensitized tissue, 2) inflammatory swelling within the eustachian tube, or 3) inflammation and edema of the nose and nasopharynx. Bernstein et al¹⁶⁰ reported that less than 15% of children with otitis media with effusion and proven respiratory allergy had detectable IgE antibodies in middle ear fluids. Even though this study did not document the onset or duration of the otitis media with effusion at the time of tympanocentesis, these data do not suggest that the middle ear functions as a primary "shock" organ in most patients with otitis media with effusion. The latter two mechanisms would implicate abnormal eustachian tube function, and recent clinical experiments in our laboratories have shown that allergic rhinitis can contribute to eustachian tube obstruction and must be considered a potential risk factor in the pathogenesis of otitis media with effusion.

To establish a causal relationship between an allergic reaction in the nose and nasopharynx and the expression of eustachian tube obstruction, a clinical investigative model using allergic patients with documented IgE-associated nasal allergy has been developed, as well as a comparable experimental passively sensitized monkey model. Employing a double-blind protocol in patients with allergic rhinitis, a provocative intranasal pollen challenge induced eustachian tube obstruction that was preceded by allergic rhinitis. A placebo challenge did not provoke eustachian tube obstruction.¹⁶¹ These results have been confirmed with the perennial inhalant allergen house dust mite, as well as the seasonal pollens ragweed and grass. Additional studies in our laboratories have shown that eustachian tube obstruction was antigen dose-dependent and related to the concentration of the patient's serum IgE antibody titer. The dose of antigen that provoked the allergic rhinitis was less than that which induced eustachian tube obstruction, but the nasal obstruction resolved sooner than eustachian tube obstruction. Antihistamines, topical intranasal aerosolized corticosteroids, or cromolyn sodium pretreatments were effective in attenuating this response.

The specific anatomic site of the inflammation associated with the development of eustachian tube obstruction in these human intranasal challenge studies has not been identified. Histamine and allergen discs applied to the anterior nasal mucosa do not consistently provoke eustachian tube obstruction. In contrast, aerosolized intranasal histamine has induced eustachian tube obstruction in patients with allergic rhinitis but not in normal subjects. These observations have been confirmed in our laboratory with a double-blind dose-response protocol that suggested a heightened responsiveness of the eustachian tube to histamine in allergic subjects. It is our hypothesis that the allergen-provoked or histamine-provoked posterior nasopharyngeal mucosal edema subsequently occludes the proxi-

mal portion of the eustachian tube. Provocative intranasal challenge with histamine or allergen (postchallenge) results in histamine's reacting with histamine receptors of the trigeminal nerve and initiating a parasympathetic neural reflex. This and the local action of mediators induce increased nasopharyngeal edema and secretions and potential eustachian tube edema. This reaction causes extraluminal eustachian tube obstruction, because the pressure exerted by the closed tube exceeds the maximum force exerted by the tensor veli palatini muscle, and the patient is unable to open the eustachian tube actively by swallowing or yawning. Thus, eustachian tube obstruction develops with inability to equilibrate middle ear pressure or drain excess middle ear or tubal secretions. In this manner we propose that allergy plays a role in the development of middle ear disease.¹⁶² A similar extraluminal tubal obstruction has been suggested in patients with infectious rhinitis and pharyngitis.

To better define the passive and active properties of the eustachian tube, our laboratories have developed an animal model. Rhesus monkeys were passively sensitized to ragweed with human serum with high levels of IgE antibody to ragweed pollen.¹⁶³ Following intranasal pollen challenge the passively sensitized monkeys developed allergic rhinitis and eustachian tube obstruction. With use of the inflation-deflation and forced-response tests via inserted tympanostomy tubes, active tubal function was markedly impaired, but passive resistance increased only slightly. To better define the relationship between allergic rhinitis and eustachian tube obstruction, nonsensitized rhesus monkeys were challenged with increasing doses of intranasal histamine.¹⁶⁴ It was hypothesized that intranasal histamine challenge would result in eustachian tube obstruction similar to that observed in the prior intranasal antigen challenge studies. Not only did rhinitis and increased active resistance within the eustachian tube develop, but passive resistance also increased. These data indicate that the intranasal histamine provoked not only extraluminal obstruction but also intraluminal obstruction. Therefore, these studies have confirmed and extended our human studies.

Because the doses of intranasal allergen needed to provoke eustachian tube obstruction were considerably more than would be inhaled naturally, it is appropriate to question the clinical relevance of these experimental studies. Preliminary observations of a small group of children with allergic rhinitis and a past history of otitis media with effusion who had weekly monitoring of eustachian tube function suggest an increased frequency of eustachian tube obstruction during a well-defined pollen season. However, similar studies in young adults without a history of ear disease have not shown any increased frequency of eustachian tube obstruction during pollen season. Thus, the clinical correlates of nasal allergy and concomitant eustachian tube obstruction as well as otitis media with effusion need to be established.

Specific Factors

BREAST-FEEDING AS PREVENTION FOR OTITIS MEDIA

PHILLIP H. KALEIDA, MD

INTRODUCTION

Published reports comparing infant feeding modes with morbidity or mortality or both have been available for at least 75 years.¹⁶⁵⁻¹⁶⁸ Many recent studies have examined a potential relationship between breast-feeding (BF) versus cow's milk-based bottle feeding and middle ear disease in children. In this report, several selected studies^{168,75,169-177} are reviewed critically, and suggestions for future investigations are presented.

REVIEW OF STUDIES

Chandra¹⁶⁹ evaluated 70 infants in rural India, of whom half received only BF for 2 or more months (mean, 4.8 months) and half received only cow's milk or buffalo's milk by bottle. Weekly home visits were made by a trained nurse. A separate cohort of 60 urban Canadian infants was also studied. Half of these subjects were initially only breast-fed for 2 or more months (mean, 3.6 months), and half were given cow's milk. The families were telephoned every 2 weeks. The method of subject selection was not stated. The definition of otitis media was "mucopurulent discharge from (the) external auditory meatus, with or without fever, irritability, and pulling at ears." Most illnesses were documented by examination. During the 12-month follow-up of the Indian infants, 21 and 52 bouts of otitis media developed in the breast-fed and formula-fed groups, respectively ($p < .001$). During the 24-month follow-up of the Canadian children, otorrhea was also observed less often in the breast-fed (9 bouts) compared with the bottle-fed (86 bouts) group ($p < .001$). Although they were matched for socioeconomic variables, education of the parents, and size of the family, it is unknown whether the groups were similar regarding distribution of sex, day-care exposure, and atopy. The outcome measure was gross (otorrhea), and intact middle ears with effusion presumably were not detected or not counted. The number of subjects in each group who experienced episodes of otorrhea and the time of occurrence of otitis media relative to active BF were not stated.

Saarinen⁷⁵ enrolled 256 healthy ($\geq 3,000$ g birth weight) Finnish infants from primarily upper middle class families (volunteers). "Long BF" was defined as 6 or more months of breast milk without cow's milk. The "cow's milk group" included infants who were initially breast-fed for less than 2 months. There was also an "intermediate (by duration) BF" group. Otitis media was defined, but pneumatic otoscopy was apparently not performed. The author, aware of the feeding method, examined and treated most of the infants until 1 year of age. Multiple physicians provided subsequent care. Maternal history and medical record review were used to determine illness of children between 1 and 3 years of age. During the initial 6 months, none of 57 infants in the long BF group, compared with 10 (10%) of 105 infants in the cow's milk group, developed otitis media ($p < .05$). From birth to 1 year of age, 3 (6%) of 53 infants in the long BF group compared with 18 (19%) of 96 subjects in the cow's milk group developed two or more bouts

of otitis media ($p < .05$). From 1 to 3 years of age, 2 (6%) of the 33 long BF children compared with 17 (26%) of the 65 cow's milk-fed children had four or more episodes of otitis media ($p < .05$). Results in the intermediate BF group for the three age-otitis media categories were 2 (3%) of 78 children, 7 (10%) of 73 children, and 5 (11%) of 45 children, respectively. The author did not state the rationale for selection of these particular age-otitis media categories. The feeding groups were similar regarding parents' professions and in both the percentages of subjects cared for in the home and without siblings of school age. Information was not provided concerning comparability of the groups in regard to sex, atopy, or actual observation frequencies.

Pukander and colleagues¹⁷⁰ compared a group of 264 Finnish children who had acute otitis media with a control group of 207 similar-aged children. Breast-feeding for 1 to 3 months was associated with a lower proportion of children who developed acute otitis media, compared with BF for less than 1 month. The definition of otitis media was provided in the report. Incidence of otitis media and risk factors were determined, however, by a retrospective questionnaire. It was not stated whether the group breast-fed for less than 1 month and the groups breast-fed for longer intervals differed in other important characteristics.

Teale and co-workers¹⁷¹ studied 1,011 Boston infants who had one or more bouts of acute otitis media during the 27 months after their birth. Significantly smaller percentages of breast-fed children compared with bottle-fed children had middle ear effusion at 30, 60, 90, and 120 days after the first episode of acute otitis media. It was not stated whether children with prolonged BF were receiving formula or solids concurrently. There was no significant difference in the number of episodes of acute otitis media according to feeding category.¹⁷² Information was not provided in the published abstract comparing day-care exposure, socioeconomic status, or frequency of nasal congestion in each group, nor were data concerning the number and "validation" of the otoscopists.

In children with cleft palates, Paradise and Elster¹⁷³ reported that during the first 18 months of follow-up, 11 (37%) of 30 infants receiving breast milk (exclusively or in addition to cow's milk), compared with none of 222 formula-fed infants, had at least one pneumatic otoscopic examination in which middle ear effusion was absent unilaterally or bilaterally ($p < .0001$). The frequency of observation in each feeding group was equivalent (J. L. Paradise, personal communication, 1986). The duration of the effusion-free period and the determination of outcome versus length of exclusive and partial BF were not reported in the published abstract. That breast milk was generally supplied by an artificial feeder suggests that milk content rather than another mechanism may be important.

Of 209 infants, not breast-fed, from "families of lower educational status" in rural New York, Cunningham¹⁷⁴

noted that 21 (10%) developed otitis media between birth and 4 months of age, whereas not 1 of 45 breast-fed subjects did so ($p < .05$). For the 503 total subjects from all socioeconomic strata (99% white) followed for 12 months, he found 3.7 compared with 9.1 episodes of otitis media per 1,000 patient-weeks in the groups receiving one or more BF and "artificial" feeding, respectively, at the time of the illness ($p < .001$).¹⁷⁵ The author acknowledged the possibility of age bias inherent in all such studies. Feeding methods, but not otitis media, were defined; data pertaining to both were based on medical record review. Pneumatic otoscopy was not always used.¹⁷⁴ It is unclear whether the frequency of observations in each group was similar. In an earlier report, Cunningham¹⁷⁶ found no statistically significant difference in episodes of otitis media per 1,000 patient-weeks from birth to 1 year in a group being breast-fed (3.4) compared with a group being artificially fed (6.3) when otitis media developed ($p < .10$). Some of the bottle-fed infants had been breast-fed initially. The contribution of repeatedly ill children to the total episodes of illness was addressed, but the specific data regarding otitis media were not provided.

In 279 infants (younger than 1 year of age at entry) in Baltimore, 86% of whom were black, Fosarelli and colleagues¹⁷⁷ reported that 52% of 46 breast-fed infants did not develop otitis media during the 12-month follow-up period, compared with 32% of 233 bottle-fed infants ($p = .05$). Interviews were used to obtain information regarding feeding and otitis media. Illness was ascertained by review of medical charts and computerized records. Criteria for otitis media were provided, but BF was not defined. Whether or not the feeding groups were comparable in important variables related to otitis media was not stated.

Kraemer and co-workers⁴⁸ compared Seattle children admitted to a surgical ward for tympanostomy tube placement because of persistent effusion (cases) with those admitted for other reasons (controls) and matched them for age, sex, and surgery month. There was no significant difference between cases and controls in the percentage of subjects exclusively breast-fed or bottle-fed for 6 months after birth (obtained by retrospective interview). Again, measurement (recall) bias may have existed.

Finally, in several other studies^{73,178-182} (with differing results), some of the design flaws and biases discussed in this report were overtly or potentially present. Holmes and

colleagues¹⁸² reported that in their study population the level of education of the mother (not feeding mode) was inversely associated with the number of overall infections during the first year of life. Their sample consisted of white, full-term infants who had four or more "regular clinic appointments" during the follow-up period and on whom "adequate" information had been obtained. Subjects in all three feeding categories appeared to have, however, a low incidence of acute otitis media.

FUTURE RESEARCH

In order to circumvent the methodologic and analytic limitations of many previously published studies, future investigations probably will require relatively large sample sizes, as well as even distribution or matching of important variables and the use of appropriate statistical tests. A prospective study of a generally "homogeneous" population would appear to be advantageous. The method of subject selection and exclusion criteria must be explicit, because BF and bottle-feeding cannot be allocated. Breast-feeding should be defined in terms of exclusiveness, duration, feeding position, and medical or other reason for alternatives. Criteria for otitis media must be known, and a uniform management protocol developed. Factors such as laterality of otitis media and nasal congestion may be important. Observations that are equivalent, regular, frequent, valid, reliable, and preferably "blinded" for each feeding group are required. Attrition must be examined, and consideration given to the fact that the composition of the feeding groups changes over time (a decreasing proportion of breast-fed infants). Finally, a precise mechanism of action must be fully elucidated. Difficulties encountered in BF research have been addressed elsewhere.¹⁸³⁻¹⁸⁸

SUMMARY

Breast-feeding is currently the generally preferred method of infant feeding.¹⁸⁹⁻¹⁹¹ Published reports to date concerning "protective" benefits of BF in regard to otitis media in children have had differing conclusions, but in several a favorable association was suggested. The major methodologic limitations evident in selected studies have been discussed in this report. Future investigations may define better the impact (if any) of BF on upper respiratory tract infection (which often precedes otitis media) and should evenly distribute, match, eliminate (if possible) or control in the analysis for potential or known confounding variables.

HEREDITARY AND ENVIRONMENTAL FACTORS IN OTITIS MEDIA

JEROME O. KLEIN, MD

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Risk for single and recurrent episodes of acute otitis media and otitis media with effusion is associated with a variety of host and environmental factors. Host factors include anatomic, physiologic, and immunologic conditions that may be governed by hereditary mechanisms. Environmental factors include housing and day-care that may increase exposure to microorganisms or antigens and climatic conditions such as extremes of temperature, humidity, and altitude that may increase the pathogenici-

ty of these organisms or antigens. This brief review focuses on the role of selected hereditary factors (race, family studies) and environmental factors (climate and day-care). Elsewhere in this Supplement, authors discuss information about anatomic defects (cleft palate, Down syndrome, and congenital facial abnormalities), allergy, and breast-feeding. A more complete review of environmental and hereditary conditions with extensive bibliography has been provided.¹⁰⁴

HEREDITARY FACTORS

Children who have problems with infections of the middle ear are likely to have disease early in life. Boston children who had first episodes of acute otitis media in the first year of life were four times as likely to have three or more infections in the next 24 months as were children who had a first episode of otitis at 2 years of age; children who had initial acute otitis media by 2 months of age were six times as likely to have three or more infections in the next 24 months as were children who had a first episode of otitis media at 18 months of age.¹⁰⁴ These data suggest that an underlying anatomic, physiologic, or immunologic dysfunction of the upper respiratory tract, most likely including the eustachian tube, is identified by the occurrence of infections early in life.

Race. American Indian, Alaskan and Canadian Eskimo, Australian aboriginal, and African children have a high incidence of acute otitis media. The disease is often severe and represented by chronic otorrhea, destruction of the tympanic membrane and ossicle, and other forms of a necrotizing process in the middle ear. The experience in these children is discussed elsewhere in this Supplement by Stewart (p 20), Todd (p 22), Canterbury (p 23), and Dever et al (p 25).

Black American children appear to have less disease due to middle ear infection than do white American children. Black children have been noted to have significantly less ear disease, less impairment of hearing, a decreased incidence of acute otitis media, and a decreased incidence of persistent middle ear effusion.

In a study of Cleveland children during the first year of life, acute otitis media occurred significantly less frequently in black when compared with white children.¹¹¹ The higher incidence of ear disease in white children or lower incidence in black children is not readily explained. Significant differences in the length, width, and angle of the eustachian tube in skulls of black Americans, white Americans, and American Indians implicate an anatomic basis for racial predisposition to or protection from otitis media.⁸⁰ A physiologic basis for racial predilection for otitis media is suggested by the results of eustachian tube inflation-deflation tests: American Indians had lower forced opening pressures than had been measured previously in a group of white subjects.¹⁹² Although the racial differences may be real, poverty is a common factor among many of the nonwhite populations that have been tested, and social and economic variables need to be considered in inter-

racial studies.

Familial Factors. Boston children who had single or recurrent episodes of otitis media were more likely to have siblings with histories of chronic otitis media than were children who did not have problems with otitis media.¹⁰⁴ Adopted Apache children had more episodes of acute otitis media than their non-Apache siblings and had a rate of otitis media similar to that of Apache children who remained on the reservation.¹⁹³

ENVIRONMENTAL FACTORS

Social and Economic Conditions. Variables identified as important in studies of respiratory tract infections may be of importance in the causation of otitis media. These include crowded living conditions, poor sanitation, inadequate hygiene, and inadequate medical care.

Climate and Season. Extremes of temperature, humidity, and altitude may play a role in respiratory tract infections. The seasonal incidence of infections of the middle ear parallels the seasonal variations of upper respiratory tract infections. Acute episodes peak during the winter, are frequent in the fall and spring, and are least frequent in the summer.

Day-Care. There is ample opportunity for spread of respiratory tract infections among children attending day-care. Coughing and sneezing at close range is common. Rhinovirus and respiratory syncytial virus can remain infective for hours to days in secretions on nonporous materials such as toys, or for more than 30 minutes on cloth or paper tissues saturated with secretions. Data about the relative risk of otitis media in children in day-care compared with children cared for at home are limited. Studies in Denmark, Finland, and Sweden suggest a higher incidence of acute otitis media and an increased prevalence of middle ear effusion in children attending large-group day-care compared with children cared for at home. No equivalent data about American children are available. More data are needed to determine the importance of the multiple factors that relate to the role of day-care in recurrent and severe otitis media and its association with problems in development of speech and language. In addition to increased exposure to communicable infections, factors to be considered in analyses include differences in socialization and peer interaction, amount and quality of language, and hearing impairment associated with middle ear effusion. The most current and complete information on infectious disease in child day-care was provided in 1986.¹⁹⁴

Special Populations

OTITIS MEDIA IN INFANTS AND CHILDREN WITH CLEFT PALATE: CURRENT EPIDEMIOLOGIC ISSUES

JACK L. PARADISE, MD

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Two decades have elapsed since the initial observations in Philadelphia¹⁹⁵ and in Pittsburgh¹⁹⁶ that in infants and young children with unrepaired cleft palate, middle ear effusions are the rule. Similar observations subsequently have

been reported from Germany,¹⁹⁷ the Netherlands,^{198,199} Norway (P. Møller, Otopathology and hearing loss in cleft palate patients during the first 15 years of life, unpublished observations, 1973),²⁰⁰ England,^{201,202} Switzer-

land,²⁰³ France,²⁰⁴ Japan,²⁰⁵ and Italy,²⁰⁶ as well as from various centers in the United States.²⁰⁷⁻²¹⁰

Regarding the high prevalence of middle ear disease and hearing loss in patients with cleft palate irrespective of age, previous reviews²¹¹⁻²¹³ have summarized the literature prior to 1975. Since then, reports concerning these relationships have continued to appear from this and other countries.^{200-206,208,209,214-218} Unfortunately, these reports show much variability in case selection, examination procedures, diagnostic definitions, the extent of information provided regarding prior medical and surgical treatment, and methods of statistical analysis. For that reason the reports are limited in comparability and in the new epidemiological information they provide. Nonetheless, taken together the reports serve to reconfirm that in infants with cleft palate, otitis media with effusion is virtually universal, that it tends to decline with increasing age but remains prevalent into adulthood, and that hearing impairment is not infrequently either a transient accompanying complication or a permanent sequela.

There appear to be six epidemiological issues of current interest regarding relationships between the cleft palate condition and the occurrence of otitis media.

How Much Hearing Loss Accompanies Otitis Media in Cleft Palate Infants? It generally has been assumed that middle ear effusion in infants with cleft palate is accompanied by conductive hearing loss. However, this assumption has remained questionable, since audiometric data regarding young infants with effusion generally have been scant, and since in older children with effusion, hearing loss is sometimes minimal.^{113,219} Recently, Fria et al²²⁰ administered auditory brain stem response tests to a group of young cleft palate infants immediately before they underwent myringotomy with tympanostomy tube placement. All but one showed mild loss (hearing threshold, 20 to 35 dB) or moderate loss (hearing threshold, 40 to 55 dB) in one or both ears. On retesting immediately following tube placement, most of the ears with hearing loss preoperatively no longer showed a loss or, in a few cases, showed a reduction from moderate to mild loss. These findings support the inference that specifically in infants with cleft palate, middle ear effusion usually does cause conductive hearing loss.

Is Otitis Media in Infants With Cleft Palate Indeed Invariable? In a series of studies over the past two decades at the University of Pittsburgh Cleft Palate Center, we have been examining infants at frequent intervals from soon after birth and have been recording detailed otoscopic findings. During much of this period we also happened to have been recording detailed feeding histories in a separate study of feeding and nutrition. One of the study's findings was the consistent inability of mothers to successfully breast-feed infants with cleft palate. Having sporadically encountered infants who seemed doubly unusual in that they not only had normal otoscopic findings in one or both ears but also were receiving breast milk — expressed manually by the mother and provided via an artificial feeder²²¹ — we reviewed feeding and otoscopic data for the 252 infants enrolled in our program over an 8-year period.

Two hundred twenty-two (88.1%) of the infants had received cow's milk or soy formulas with no reported admixture of breast milk, whereas 30 infants (11.9%) had been provided breast milk — in virtually all instances via

an artificial feeder — exclusively or in part for varying periods, many quite brief. In the 222 infants fed only formula, no ear was recorded as effusion-free at any examination during the first 18 months of life. By contrast, in the 30 infants fed any quantity of breast milk, 11 had one or both ears recorded as effusion-free at one or more examinations ($p < .0001$).¹⁷³

These findings constitute evidence that in infants with unrepaired cleft palate, middle ear effusion is not necessarily invariable. The findings have additional implications: they suggest that impaired eustachian tube function is not the sole factor in the pathogenesis of otitis media in infants with cleft palate, and they support the hypothesis that in infants generally, breast milk provides protection against the development of otitis media. (Subsequently we have encountered two cleft palate infants not fed breast milk who also have shown normal otoscopic findings from time to time during the first year of life.)

It seems important to note here that the absence of demonstrable middle ear effusion may not exclude the presence of otitis media. Møller and Dalen²²² described a 2-month-old cleft palate infant who was found at myringotomy to have air in both middle ears but whose middle ear mucosal biopsy findings on scanning electron microscopy were indistinguishable from those of cases of secretory otitis media. Within a few months the infant went on to develop bilateral middle ear effusion. Similarly, we^{207,220,223} and others^{208,224-227} have reported occasional infants who have otoscopic or tympanometric evidence, or both, of middle ear effusion, but who at myringotomy were not found to have effusion. Possible explanations for such a discrepancy have been discussed previously.^{207,224,226,227}

Is Later Occurrence of Otitis Media in Children With Cleft Palate Influenced by Type of Early Management? Various reports have suggested, with evidence of varying strength, that otologic status improves following palate repair early in life.^{199,208,207-209} That the effect is not dramatic, however, is illustrated by the experiences of a group of 24 children, all of whom had received initial myringotomy with tube placement by 1 year of age and soft palate repair by 2 years of age.²²⁸ When the children were studied at 5 to 11 years of age, they had received a mean number of 3.1 subsequent myringotomy procedures; one child had received 8 subsequent procedures, and only two children had received none.

Currently, in a randomized controlled trial involving cleft palate infants, all of whom receive tympanostomy tube placement by 6 months of age, we are studying the otologic effects of early (age 6 months) versus later (age 18 months) soft palate repair and of continuous antimicrobial prophylaxis.

What Are Long-Term Implications of Otitis Media in Infants and Children With Cleft Palate? We recently addressed this question by comparing 24 closely matched pairs of children with repaired palatal clefts whose overall treatment had been equivalent except regarding otitis media during early life. One group — mentioned above — had undergone initial myringotomy with tube placement early (mean age, 3 months), whereas the other group had undergone initial tube placement either later (mean age, 30.8 months) or not at all, and thus presumably had had middle ear effusion throughout most or all of the first few years of life.

When studied at 5 to 11 years of age, the two groups

were closely similar regarding otoscopic and tympanometric findings. Eardrum scarring was common in both groups. Hearing acuity was impaired somewhat in both groups, but slightly more so in the group undergoing later initial myringotomy. Consonant articulation also was impaired in both groups, but substantially more impaired in the group undergoing later initial myringotomy. Mean verbal, performance, and full-scale intelligence quotients and scores on psychosocial indices were normal in both groups and did not differ significantly between the groups.²²⁸

These findings in children with cleft palate also would appear to bear on the question of whether, in children generally, lasting adverse effects result from otitis media with effusion limited to the early months or years of life.²²⁹ The findings support hypotheses that early, long-standing otitis media may result in later impairments of hearing and of speech, although it is important to note that otitis media as protracted as in infants and young children with cleft palate must occur relatively rarely in the general population of children. The study's findings do not support hypotheses that otitis media limited to the early years of life may adversely affect later cognitive, linguistic, social, and emotional development.

Hearing loss that is definitely sensorineural in nature has been reported in young adults with cleft palate.^{230,231} In cleft palate children, extra-high-frequency hearing loss — in the range of 8,000 to 20,000 Hz — has recently been described,²¹⁷ but whether it was conductive or sensorineural was not determined. Whether sensorineural loss in cleft palate patients is a consequence of middle ear disease or occurs on some other basis remains unclear.

To What Extent Are Long-term Otologic Sequelae in Children With Cleft Palate Attributable to Otitis Media Rather Than to Treatment of Otitis Media? Early tympanostomy tube placement in infants with cleft palate offers immediate resolution of effusion and improvement in hearing, but risks the frequent development of purulent otorrhea that may be resistant to treatment, and also the frequent development of substantial eardrum scarring.^{200,228,232} Thus, in a group of 15-year-old patients with repaired cleft palate, Møller²⁰⁰ found 79 of 114 (69%) eardrums that had never received tubes to be otoscopically normal, compared with none of 22 eardrums that had received tubes. These findings underscore the possibility that some of the later otologic findings in cleft palate children might be due to treatment measures undertaken for otitis media rather than to otitis media itself.

What Is the Pattern of Occurrence of Otitis Media in Patients With Submucous Cleft Palate? No systematic study of this question appears to have been reported. In series of selected patients with either submucous cleft palate or bifid uvula or both, the proportions of patients with histories or findings of middle ear disease have ranged from 34% to 80%.^{203,233-236} Clearly, patients with submucous clefts deserve close and continuing observation for the occurrence of otitis media.

The six epidemiologic issues discussed here also contain important implications regarding both the pathogenesis and the management of otitis media in infants and children with cleft palate. Such individuals constitute an important population in whom otitis media appears as a virtual given, and from whom lessons learned may prove translatable to the childhood population at large.

OTITIS MEDIA IN A SCHOOL FOR DEAF CHILDREN: AN 8-YEAR STUDY

HELEN B. CRAIG, PhD; SYLVAN E. STOOL, MD

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INTRODUCTION

Over the past 9 years, an otologic evaluation and maintenance program has been conducted at the Western Pennsylvania School for the Deaf (WPSD), both to establish incidence figures on middle ear problems in this population and to provide early treatment and prevention for the problems identified. Longitudinal data on the first 8 years have been analyzed and present a very consistent picture of middle ear status among deaf preschool children and schoolchildren. The information gathered over this extended period is of special value, because both the student population and the evaluation methodology remained relatively constant, providing a very stable data base for recommendations of otologic assessment and care among such children.

POPULATION

The population for this study comprised all students enrolled in the WPSD from 1977 through 1985, with an average of 359 students per year, ranging from 2 to 21 years of age. The majority of these students (77%) were profoundly deaf (>90 dB), with a mean hearing loss

schoolwide of 97 dB ANSI; 56% were male, 44% female; 79% lived at school 5 days per week, 21% went home daily.

In this population, all with sensorineural hearing loss, the addition of a conductive loss can be especially devastating, reducing residual hearing by a critical 10 to 15 dB — the difference between receiving useful auditory information or useless noise. Even for children who are not deaf, the presence of a fluctuating conductive loss precipitated by otitis media with effusion has been found significantly detrimental to verbal comprehension and expression, to speech articulation, and to reading scores.^{237,238} For children whose hearing is already severely restricted, it is therefore imperative to prevent imposition of this added loss.

METHOD

The procedures for middle ear evaluation and follow-up at WPSD have been described elsewhere.²³⁹⁻²⁴¹ Briefly, the project has involved middle ear screening in the autumn and spring of each year from September 1977 through May 1986, plus monthly follow-up examinations for all

TABLE 31. FALL SCREENING RESULTS AT WESTERN PENNSYLVANIA SCHOOL FOR THE DEAF, 1977-1984

Year	Categories									
	1		2		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%
1977	254	57	135	30	13	3	31	7	12	3
1978	281	67	77	18	15	4	32	8	11	3
1979	271	67	95	24	23	6	10	2	5	1
1980	259	73	68	19	17	5	5	1	8	2
1981	204	64	72	22	22	7	15	5	7	2
1982	222	67	41	12	15	5	47	14	5	2
1983	215	68	54	17	13	4	30	10	4	1
1984	171	60	56	20	12	4	33	12	11	4
Total	1,877	65	598	21	130	5	203	7	63	2
SD	4.98		5.31		1.29		3.89		1.04	

Categories: 1 — normal, 2 — residual disease, 3 — inactive disease, 4 — high risk, 5 — disease active (urgent).

children 2 to 10 years of age and for any other students who were discovered to be "at risk" in the screening examinations or who were referred by teachers, parents, or infirmity staff. The project staff included a specially trained project nurse who conducted the daily evaluations at WPSD and a board-certified consulting otolaryngologist from the nearby Children's Hospital of Pittsburgh. Evaluation measures included both otoscopy and tympanometry, conducted with a diagnostic pneumatic otoscope and an electroacoustic impedance audiometer with an x-y plotter. Ears that were occluded with cerumen were irrigated by the project nurse so that the full examination could be conducted. During the course of the 8 years reported here, the project nurse conducted 21,750 otoscopic examinations, plotted 18,952 tympanograms, and irrigated 3,587 ears.

A serial examination and record form was designed to include all otologic and tympanometric information from the evaluations, with a designation of middle ear status by one of five categories as follows: 1) normal: no evidence of disease; 2) residual disease: healed perforation, opaque tympanic membrane; 3) inactive disease: tube in tympanic membrane, dry perforation; 4) high risk: high negative pressure (HNP) ≥ 100 mm H₂O; and 5) disease active (urgent): effusion, otorrhea. All students assigned to categories 4 and 5 received special follow-up by the consulting otolaryngologist and treatment depending upon individual need.

RESULTS

Results from each examination throughout the course of this project were systematically recorded and summarized on the standard serial examination form and were tabulated annually, with flow charts maintained on each child and each ear examined from 1977 until 1985.

Screening Results. In 8 years of fall otologic/tympanometric screening at WPSD, the percentage of children schoolwide who were assigned to each of the five categories varied only slightly (Table 31). Thus, with little variation, 65% were identified with normal middle ear status, 21% with residual disease, 5% with inactive disease, and 9% as high risk or urgent. When data are analyzed by age groups, the percentages change significantly, with 21% of preschool students (2 to 5 years old) in the high-risk or urgent categories, compared with 12% of the elementary students (6 to 12 years old) and 4% of the upper school students (13 to 21 years old). However, the high consistency across the 8 years remains true within each of these major age groups. In like manner, the yearly and

longitudinal spring screening results almost duplicate the fall screenings, with no more than a 2% differential in any one category on the long-term results.

Serial Evaluation Results. As noted, all students 2 to 10 years of age received monthly follow-up evaluations, as did older students who were at any time judged at risk or urgent or who were referred for examination. The results of these evaluations are in sharp contrast with both the fall and spring screenings, especially for the younger children. As shown in Table 32, the percentage of preschool children seen with serious middle ear problems (categories 4 and 5) was over three times as high with the serial evaluations as with the fall screening alone, and for effusions alone, the number was six times as high. If the monthly follow-ups had not been provided, only 13 preschoolers with effusions (6%) would have been discovered, compared with the 81 (38%) who were actually discovered during the serial assessments. For all children in the 2- to 10-year age range (including both preschool and lower elementary school), 64% were put in categories 4 or 5 in the serial evaluation, compared with 14% in the fall only. Although not as dramatic, the serial results for the older students (11 to 21 years old) who were so evaluated also showed a higher percentage of severe middle ear problems than did the fall screening (14% compared with 4%).

Recurrence of Middle Ear Infections. Almost all of the preschool and elementary school students who were seen at any one time with HNP (84%), with effusion (95%), or with inactive disease (100%) showed recurrent middle ear problems throughout the year. This was true for 43% of the upper school students. An analysis of the 2 to 6 years following the very first screening for any child and of his/her first year of middle ear evaluations revealed a similar pattern. Of those ears schoolwide whose status was judged as urgent during a first year, 94% returned to urgent, high-risk, or inactive disease at least once during the second year — 30% with recurrent effusion. In 21% of the ears, effusions recurred even 5 years after the initial diagnosis of urgent, reappearing from one to nine times during the interim years and alternating with HNP and inactive disease.

An initial diagnosis of inactive disease (category 3) proved almost as predictive of continued middle ear infection including effusion as an initial diagnosis of urgent. In the follow-up of ears categorized as 3s, 100% were found to rate a 3, 4, or 5 throughout the first year, 97% throughout year 2, and 59% even through year 5. Fifty percent of these developed effusions at least once during year 2 fol-

TABLE 32. COMPARISON OF FALL SCREENING AND SERIAL OTOLOGIC EVALUATIONS: "WORST-EAR" RESULTS FOR PRESCHOOL CHILDREN AT WESTERN PENNSYLVANIA SCHOOL FOR THE DEAF

Evaluation	Categories										Total	
	1		2		3		4		5			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1979-1980												
Fall	17	40	6	14	15	36	2	5	2	5	42	100
Serial	10	24	4	9	5	12	10	24	13	31	42	100
1980-1981												
Fall	20	50	5	13	11	27	2	5	2	5	40	100
Serial	8	20	1	2	5	13	10	25	16	40	40	100
1981-1982												
Fall	11	29	6	16	12	31	6	16	3	8	38	100
Serial	3	8	1	3	1	3	23	60	10	26	38	100
1982-1983												
Fall	12	32	6	16	11	30	7	19	1	3	37	100
Serial	3	8	1	3	0	0	16	43	17	46	37	100
1983-1984												
Fall	7	22	1	3	7	22	14	44	3	9	32	100
Serial	2	6	0	0	2	6	11	35	17	53	32	100
1984-1985												
Fall	7	26	5	19	10	37	3	11	2	7	27	100
Serial	1	4	5	19	3	11	10	37	8	29	27	100
Total												
Fall	74	34	29	13	66	31	34	16	13	6	216	100
Serial	27	12	12	6	16	7	80	37	81	38	216	100

Categories: 1 — normal, 2 — residual disease, 3 — inactive disease, 4 — high risk, 5 — disease active (urgent).

lowing the initial diagnosis, and 26% were still developing effusions 5 years later.

The diagnosis of HNP led to effusion in a lower percentage of cases than did a diagnosis of either category 3 or 5, although still much higher than for ratings of 1 or 2. In any one year, a rating of 4 led to effusion for 21% of the ears so rated and for 33% of the ears among children 2 to 10 years of age. On a longer-term basis, 19% of the ears measured with HNP during the first year of testing developed effusion during year 2, diminishing to 4% by year 5. In contrast, only 4% of those initially categorized as normal developed effusions even in year 1.

In addition to the analysis of recurrent effusion, a frequency count also was made of bilateral middle ear infection. Of all the students in this study who were seen with effusion in at least one ear, 84% also had an effusion in the other ear at the same time or at some other time during the same year. Sixty-eight percent of students with HNP also had both ears involved. The latter findings are in agreement with previous results in normally hearing children.²³⁸

DISCUSSION

Four common trends are evident through all 8 years of this study. First, at any one screening time, the percentage of students in each of the five middle ear categories re-

mained remarkably constant. Thus, regardless of whether a screening took place in the fall or spring, in 1977 or in 1985, approximately 65% were judged as normal, 20% as residual, 5% as inactive disease, 8% as high risk, and 2% as urgent. Second, a single fall screening proved highly inadequate as a predictor of middle ear disease for the full year, especially for children under 10 years of age, with six times as many effusions discovered in preschool children during the monthly follow-ups as during the fall screenings. Third, the incidence of middle ear problems was inversely related to age. Children 2 to 10 years of age most often were classified as high risk or urgent, and of these, the highest frequency was among the preschool group, with three fourths of the ears developing either HNP or effusion. Fourth, although the identification of middle ear status as normal was not necessarily predictive of continued normal ears, the identification of severe middle ear problems at any time during the year was predictive of continued middle ear problems in the same child and in the other ear.

The consistency of these results, based on over 40,000 systematically recorded middle ear examinations, provides a solid reference point for prediction of middle ear status within other preschool and school-age groups of deaf children, and for developing middle ear evaluation programs to serve this population.

CRANIOFACIAL DISORDERS AND OTITIS MEDIA

SYLVAN E. STOOL, MD

A group of very complex disorders affect the craniofacial-oral complex and present a challenge in management to a number of medical and allied health professionals.

The temporal bone and nasopharynx are in a key location in the skull; therefore, it is not surprising that otitis media occurs frequently in children who have major craniofacial

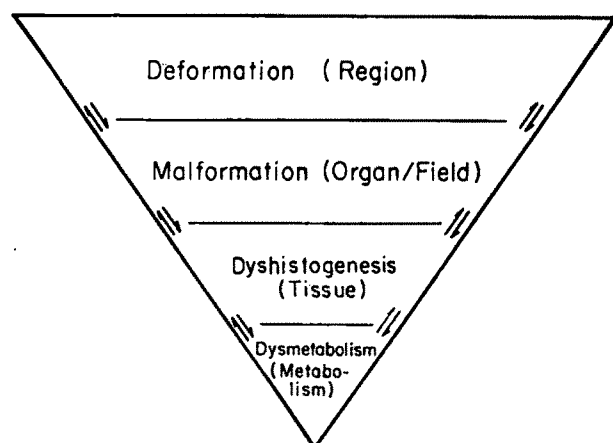


Fig 7. Stratification into dysmetabolic, dyshistogenetic, malformational, and deformational syndromes that represent expression at metabolic, tissue, organ, and regional levels, respectively. (Reprinted with permission from Cohen MM Jr. *The patient with multiple anomalies*. New York, NY: Raven Press, 1980.)

defects. The effect of otitis media with its accompanying hearing loss on total communication is obvious when we consider that these facial defects may alter communication in a number of ways. For instance, the children may be unsightly and have difficulty in establishing eye contact; therefore, visual communication is difficult; and they may have abnormalities of the speech mechanism that alter speech intelligibility. Physical diagnosis of ear disease may be hindered, because the external canals may be abnormal in size or position.

As an aid in understanding these disorders, a classification system such as that proposed by Cohen²⁴² in his text *The Child With Multiple Birth Defects* is of value. While a number of the abnormalities have been recognized as syndromes, many of the craniofacial abnormalities may be sporadic, and it is only after many similar cases have been reported that a pattern is established. Those that have been seen frequently enough to be identified as syndromes may be of either a known or an unknown genesis. The known-genesis syndromes are divided into pedigree, chromosomal, biochemical, and environmentally induced syndromes. This does not imply that we know the precise mechanism by which the defect is produced in all instances, but the manifestation may be a cluster of abnormalities that divides them into deformations, malformations, dyshistogenesis, and dysmetabolic conditions (Fig 7).

The effect on the middle ear either may be primary, such as the anatomic abnormality of structure that occurs in Treacher Collins syndrome, or may be secondary to defects in the base of the skull or airway that will influence the function of the eustachian tube and subsequently affect the ear. There are several syndrome prototypes that illustrate the value of this classification system. The prevalence of these abnormalities varies tremendously. For instance, the most prevalent is Down syndrome, which occurs in 1.5 per 1,000 persons; other syndromes such as Apert's may occur in 1 per 100,000. Some are so rare that it is difficult to establish their prevalence.

Pedigree Syndromes. Pedigree syndromes include conditions such as Apert's syndrome, Crouzon's disease, and Treacher Collins syndrome. They are usually autosomal-dominant malformations with varying penetrance and are

apparent at birth. The degree of middle ear abnormalities varies. For instance, Treacher Collins syndrome affects the branchial arch cartilages, causing ossicular abnormalities. In the other two syndromes, the middle ear may be essentially normal, but its function may be impaired because of cranial base abnormalities that result in airway obstruction or eustachian tube malformation.

An example of a pedigree syndrome that may be dyshistogenetic is cranial metaphyseal dysplasia, a condition that primarily affects bone, in which there is bone deposition without remodeling. Otitis is a frequent occurrence in these patients and is probably due to constriction of the bony eustachian tube. In this syndrome, the bone is very hard, whereas in another syndrome characterized by osteopetrosis, there is abnormal bone metabolism and the bone resembles fetal bone. It is very vascular; however, the growth of this bone may also impinge upon the lumen of the middle ear and the eustachian tube, resulting in otitis media. Achondroplasia affects the bone in the skull of cartilaginous origin and produces a very characteristic repeated-pattern syndrome in which otitis media is a frequent occurrence. Children with this disorder have normal-appearing tympanic membranes and ossicular structures. However, repeated otitis occurs, probably because of abnormal eustachian tube function due to the small nasopharyngeal airway and abnormal vectors of the tubal musculature.

There are a large number of muscular dystrophies that are pedigree in origin and affect primarily the skeletal muscle. One example is Werdnig-Hoffmann syndrome, in which there may be abnormal facies and slight abnormalities of the skull. However, the middle ear disease may have its origin in poor eustachian tube function or because the child has swallowing difficulties with nasopharyngeal regurgitation and chronic nasopharyngitis.

Chromosomal Abnormalities. The identification of chromosomal abnormalities has been explosive in recent years, and many previously described craniofacial defects are recognized as being of chromosomal origin. Most frequently encountered and therefore the most widely studied has been Down syndrome.²⁴² There have been a number of temporal bones studied from children with this syndrome, and they reveal a variety of middle ear abnormalities and a limited number of inner ear abnormalities.²⁴³ The middle ears frequently contain mesenchymal tissue and inflammation. White et al²⁴⁴ have investigated the functions of the eustachian tube in some of these children using inflation-deflation techniques and forced-response testing and have found that the dysfunction is characterized by low passive tubal resistance, a low closing pressure and constriction of the eustachian tube while swallowing, and inability to equilibrate positive and negative middle ear pressure. While the number of patients studied is small, the findings suggest that these children have a high incidence of middle ear disease because of eustachian tube dysfunction and that they should be treated aggressively to decrease a handicap effect of an additional hearing loss.

There are a number of other trisomies that have been identified and studied for middle ear disease, such as 13-15 translocational. However, many children with these trisomies have cleft palates and are well recognized as having a high prevalence of otitis media.

Biochemical Genesis. In general, children with these conditions appear normal at birth but subsequently devel-

op devastating changes. An example is mucopolysaccharidosis.²⁴⁵ Formerly, these were lumped together as gargoylism because of the grotesque facial and body deformities. Otitis media may occur because of the middle ear's becoming infiltrated with the abnormal mucoid material that results in otitis. The musculature of the eustachian tube and pharynx also may be abnormal because of the deposition of the mucopolysaccharides. In recent years, much progress has been made in understanding the mechanism of the biochemical defects. However, they are difficult to prevent and to treat.

Environmental Genesis. The conditions in this category may vary from the persistent infantile face and cranium such as that seen in fetal alcohol syndrome to the grotesque manifestations that occur in children who have amniotic bands, which may produce a variety of malformations such as facial clefts. The mechanism of otitis media in many of these syndromes is not their direct effect on the

ear, but the secondary effect from abnormal airways and alterations in the configuration of the base of the skull.

DISCUSSION

It is important to emphasize that a large number of craniofacial malformations are not well defined and that the causes have not been established. Many are so rare that the pediatrician or otolaryngologist will see only a few in his or her years of practice. However, it is also most important to provide these children with the most aggressive therapy available. Since ear disease may be cryptic because of concern with the other facial abnormalities or because the external canals are deformed, it is possible that the diagnosis of otitis media may be missed and the child will be sensory-deprived or will suffer from the effects of chronic infections. Therefore, it is most important that a program of regular examination of the tympanic membrane and intervention, whether medical, surgical, or rehabilitative, be instituted.

FUTURE DIRECTIONS

SUMMARY AND FUTURE RESEARCH NEEDS

The Workshop conferees agreed that otitis media is highly prevalent throughout the world and is predominantly a childhood disease that significantly improves with age. The highest incidence rates have been found in children 6 to 11 months of age, and the younger the child is at the first attack, the higher the risk of recurrent and chronic disease. There is a seasonal variation, with the highest prevalence occurring during the winter months and the lowest during summer, in geographic areas with a temperate climate and four seasons. These observations may be related to the seasonal variation of upper respiratory tract infections, as there is a strong correlation between upper respiratory tract infections and otitis media. The most common bacteria found in middle ear effusions are *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Branhamella catarrhalis*, with an increasing number of β -lactamase-producing strains being isolated in the latter two organisms. However, the Workshop conferees concluded that even though a great deal is known about the epidemiology and natural history of otitis media, there are still many unanswered questions. The Workshop conferees expressed concern about the following areas that need further study.

Methodology. There is a need for consistency in the definition of the disease. It is important that the sensitivity and specificity of methods used to identify the disease be established and reported. In designing a study, not only the disease but also the sample size and primary outcome measures should be defined. The design of the study also should take into account the proper statistical analysis and the representativeness of the data. Adequate attention to these factors will help ensure high cost-effectiveness and efficient use of our health care resources.

Incidence, Prevalence, and Natural History. Further studies in neonates and infants are urgently required to determine the incidence, prevalence, natural history, and associated risk factors of otitis media such as prematurity, low birth weight, and prenatal, perinatal, and postnatal medical care. Children with early onset of otitis media need to be studied in regard to incidence of bronchopulmonary, gastrointestinal, and allergic diseases.

Complications and Sequelae. More information regarding the complications of otitis media should be obtained to determine the incidence of intracranial as well as intratemporal complications. The incidence of sequelae of otitis media also should be established and correlated to specific medical or surgical treatment modalities. Short-term as well as long-term morbidity of otitis media in relation to the child's learning and development needs to be evaluated.

Microbiology. It is important to monitor the microflora within the middle ear and nasopharynx for changes in β -lactamase-producing organisms and the development of other forms or resistance. Geographic and seasonal varia-

tion in the microbiologic flora should be monitored. By use of improved culture techniques, organisms such as *Chlamydia*, *Legionella*, viruses, and other organisms should be evaluated as possible etiologic factors in otitis media.

Allergy. Further studies are required to evaluate the role of allergy in the pathogenesis of otitis media. The clinical correlations among nasal allergy, concomitant eustachian tube obstruction, and otitis media should be established, as well as the possibility that the middle ear mucosa responds functionally as a sensitized tissue. A more complete understanding of immunologic host factors that may predispose to or prevent otitis media is needed.

Specific Factors. The protective benefits of breast-feeding versus bottle feeding in regard to otitis media need further evaluation in terms of duration, exclusiveness, and feeding position. The impact on upper respiratory tract infections must be defined, and the precise mechanism of action should be fully elucidated.

Socioeconomic and environmental factors that are important in the causation of otitis media should be identified, such as the type of housing and day-care. Crowded living, poor sanitation, and poor hygiene might increase exposure to microorganisms. Climatic conditions such as extreme temperature, humidity, air pollution, and smoking may affect the host resistance to infections. The importance of nutritional status and medical care needs to be assessed, also.

Host factors such as anatomic, physiologic, and immunologic conditions that might predispose to or protect from otitis media need to be identified. The influence of heredity and racial differences, ie, eustachian tube anatomy and physiology, can be evaluated. We must assess also the possibility of a hereditary mechanism within the family.

Studies of special populations such as children with cleft palate or other craniofacial abnormalities may contain important implications regarding both the pathogenesis and the management of otitis media that can be applied to the population at large.

Conclusion. Better knowledge of the incidence, prevalence, natural history, and associated risk factors of otitis media should improve our understanding of the causes and pathogenesis of this disease. This information would allow for earlier identification and treatment of children at risk, which should prevent the possible complications and sequelae of otitis media such as learning and developmental problems. The Workshop conferees concluded that we know a great deal more about the epidemiology of otitis media today than ever before, but that more research is needed to answer the remaining important questions so that more effective methods of prevention and management can be developed.

REFERENCES

1. Bluestone CD, Cantekin EI. Design factors in the characterization and identification of otitis media and certain related conditions. *Ann Otol Rhinol Laryngol* 1979;88(suppl 60):13-28.
2. Cantekin EI, Bluestone CD, Fria TJ, Stool SE, Beery QC, Sabo DL. Identification of otitis media with effusion in children. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):190-5.
3. Feinstein AR. Clinical biostatistics XXXI: on the sensitivity, specificity, and discrimination of diagnostic tests. *Clin Pharmacol Ther* 1975;17:104-16.
4. Sackett DL, Holland WW. Controversy in the detection of disease. *Lancet* 1975;2:357-9.
5. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;299:926-30.
6. Sox HC. Probability theory in the use of diagnostic tests: an introduction to critical study of the literature. *Ann Intern Med* 1986;104:60-6.
7. Colton T. Statistics in medicine. Boston, Mass: Little, Brown, 1974:131-6, 169-73.
8. Bourke GJ, Daly CE, McGilvray J. Interpretation and uses of medical statistics. 3rd ed. Boston, Mass: Blackwell Scientific Publications, 1985.
9. Gore SM, Jones IG, Rytter EC. Misuse of statistical methods: critical assessment of articles in BMJ from January to March 1976. *Br Med J* 1977;1:84-7.
10. Billewicz WZ. The efficiency of matched samples: an empirical investigation. *Biometrics* 1965;21:623-43.
11. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 1947;12:153-7.
12. Cochran WG. The comparison of percentages in matched samples. *Biometrika* 1950;37:256-66.
13. Fleiss JC. Statistical methods for rates and proportions. New York, NY: John Wiley and Sons, 1973:72-91.
14. Hollander M, Wolfe DA. Nonparametric statistical methods. New York, NY: John Wiley and Sons, 1973:27-49, 138-84.
15. Siegel S. Nonparametric statistics for the behavioral sciences. New York, NY: McGraw-Hill, 1956:61-94, 159-73.
16. Winer BJ. Statistical principles in experimental design. 2nd ed. New York, NY: McGraw-Hill, 1971:676-84.
17. Lehmann EL. Nonparametrics: statistical methods based on ranks. San Francisco, Calif: Holden-Day, Inc, 1975:279-81.
18. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. Belmont, Calif: Lifetime Learning Publications, 1985:377-402.
19. Morrison DF. Multivariate statistical methods. New York, NY: McGraw-Hill, 1967:141-8.
20. Laird NM, Ware JH. Random-effect models for longitudinal data. *Biometrics* 1982;38:963-74.
21. Harris RJ. A primer of multivariate statistics. New York, NY: Academic Press, 1975:125-7.
22. Grizzle JE, Allen DM. Analysis of growth and dose response curves. *Biometrics* 1969;25:357-81.
23. Rao CR. The theory of least squares when the parameters are stochastic and its application to the analysis of growth curves. *Biometrika* 1965;52:447-58.
24. Hui SL. Curve fitting for repeated measurements made at irregular time points. *Biometrics* 1984;40:691-7.
25. Azzalini A. Estimation and hypothesis testing for collections of autoregressive time series. *Biometrika* 1984;71:85-90.
26. Ware JH. Linear models for the analysis of several measurements in longitudinal studies. *Am Stat* 1985;39:95-101.
27. Stiratelli R, Laird N, Ware JH. Random-effects models for serial observations with binary response. *Biometrics* 1984;40:961-71.
28. Anderson DA, Aitkin M. Variance component models with binary response: interviewer variability. *R Stat Soc J* 1985;B47:203-10.
29. Ochi Y, Prentice RL. Likelihood inference in correlated probit regression. *Biometrika* 1984;71:531-43.
30. Koch GG, Landis JR, Freeman JL, Freeman DH, Lehmann RB. A general methodology for the analysis of repeated measurements of categorical data. *Biometrics* 1971;33:133-58.
31. Cox DR. The analysis of binary data. London, England: Methuen, 1970.
32. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
33. Remington RD, Schork MA. Statistics with application to the biological and health sciences. Englewood Cliffs, NJ: Prentice-Hall, 1979:244-6.
34. Rosner B. Multivariate methods in ophthalmology with application to other paired data situations. *Biometrics* 1984;40:1025-35.
35. Rosner B. Statistical methods in ophthalmology: an adjustment for the intraclass correlation between eyes. *Biometrics* 1982;38:105-14.
36. Ederer F. Shall we count numbers of eyes or numbers of subjects? *Arch Ophthalmol* 1973;89:1-2.
37. Donner A. Linear regression analysis with repeated measurements. *J Chronic Dis* 1984;37:441-8.
38. Gail MN, Wieand S, Piantadosi S. Biased estimates of treatment effect in randomized experiments with nonlinear regressions and omitted covariates. *Biometrika* 1984;71:431-44.
39. Senturia BH, Bluestone CD, Klein JO, Lim DJ, Paradise JL. Report of the ad hoc committee on definition and classification of otitis media and otitis media with effusion. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):3-4.
40. Bluestone CD. State of the art: definitions and classification. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:1-4.
41. Rockette HE, Bluestone CD. Statistical considerations in clinical trials of otitis media. Proceedings of the Extraordinary Symposium on Otitis Media. *Auris Nasus Larynx* 1985;12(suppl 1):249-51.
42. Louis TA, Lavori PW, Bailar JC III, Polansky M. Cross-over and self-controlled designs in clinical research. *N Engl J Med* 1984;310:24-31.
43. To SS, Paher AL, Robin PE. A prospective trial of unilateral grommets for bilateral secretory otitis media in children. *Clin Otolaryngol* 1984;9:115-7.
44. Lildholt T. Ventilation tubes in secretory otitis media: a randomized controlled study of the cause, the complications, and the sequence of ventilation tubes. *Acta Otolaryngol [Suppl] (Stockh)* 1983(suppl 398):5-27.
45. Virolainen E, Puhakka H, Aantaa E, Tuohimaa P, Ruuskanen O, Meurman OH. Prevalence of secretory otitis media in seven to eight year old school children. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):7-10.
46. Tos M, Holm-Jensen S, Stangerup S-E, Sorensen CH. Changes in point prevalence of secretory otitis in preschool children. *ORL J Otorhinolaryngol Relat Spec* 1983;45:226-34.
47. Fiellau-Nikolajsen M. Tympanometry in three-year-old children. The 3-year follow-up of a cohort study. *ORL J Otolaryngol* 1984;9:115-7.

rhinolaryngol Relat Spec 1981;43:89-103.

48. Kraemer MJ, Richardson MA, Weiss NS, et al. Risk factors for persistent middle-ear effusions. *JAMA* 1983;249:1022-5.

49. Visscher W, Mandel JS, Batalden PB, Russ NJ, Giebink GS. A case-control study exploring possible risk factors for childhood otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:13-5.

50. Van Cauwenberge PB, Kluyskens PM. Some predisposing factors in otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:28-32.

51. Tos M, Poulsen G, Hancke AB. Screening tympanometry during the first year of life. *Acta Otolaryngol (Stockh)* 1979;88:388-94.

52. Tos M, Poulsen G. Tympanometry in 2-year-old children. Seasonal influence of frequency of secretory otitis and tubal function. *ORL J Otorhinolaryngol Relat Spec* 1979;41:1-10.

53. Tos M, Holm-Jensen S, Sorensen CH, Mogensen C. Spontaneous course and frequency of secretory otitis in four-year-old children. *Arch Otolaryngol* 1982;108:4-10.

54. Tos M. Epidemiology and spontaneous improvement of secretory otitis. *Acta Otorhinolaryngol Belg* 1983;37:31-43.

55. Tos M. Epidemiology and natural history of secretory otitis. *Am J Otol* 1984;5:459-62.

56. Tos M, Stangerup S-E, Andreassen UK, Hvid G, Thomsen J, Holm-Jensen S. Natural history of secretory otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:36-40.

57. Kudrjavcev T, Schoenberg BS. Otitis media and developmental disability. Epidemiologic considerations. *Ann Otol Rhinol Laryngol* 1979;88(suppl 60):88-98.

58. Hinchcliffe R. Epidemiological aspects of otitis media. In: Glorig A, Gerwin K, eds. Otitis media: proceedings of the national conference. Springfield, Ill: Charles C Thomas, 1972:36-43.

59. Teele DW, Klein JO, Rosner BA. Epidemiology of otitis media in children. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):5-6.

60. Giebink GS. Epidemiology and natural history of otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:5-9.

61. Pukander J, Sipilä M, Karma P. Occurrence of and risk factors in acute otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:9-13.

62. Ingvarsson L, Lundgren K, Olofsson B, Wall S. Epidemiology of acute otitis media in children. *Acta Otolaryngol [Suppl]* (Stockh) 1982(suppl 388).

63. Ingvarsson L, Lundgren K, Olofsson B. Epidemiology of acute otitis media in children — a cohort study in an urban population. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:19-22.

64. Lundgren K, Ingvarsson L, Olofsson B. Epidemiologic aspects in children with recurrent acute otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:22-5.

65. Ingvarsson L, Lundgren K, Olofsson B. Epidemiology of acute otitis media in children in an urban population. *Auris Nasus Larynx* 1985;12(suppl 1):105-7.

66. Ingvarsson L, Lundgren K, Stenstrom C, Olofsson B, Wall S. The epidemiology of acute otitis media. In: Sadé J, ed.

Acute and secretory otitis media. Amsterdam, the Netherlands: Kugler Publications, 1987.

67. Pukander J, Karma P, Sipilä M. Occurrence and recurrence of acute otitis media among children. *Acta Otolaryngol (Stockh)* 1982;94:479-86.

68. Klein JO. Otitis media with effusion and development of speech and language. In: Bluestone CD, Doyle WJ, eds. Eustachian tube function: physiology and role in otitis media. Workshop report. *Ann Otol Rhinol Laryngol* 1985;94(suppl 120):53-4.

69. Aine R, Kataja M, Alavaikko M. Prognostic factors for non-cleaved follicular center-cell lymphomas and immunoblastic sarcoma. A Bayesian approach. *Scand J Haematol* 1984;32:475-87.

70. Pukander J. Clinical features of acute otitis media among children. *Acta Otolaryngol (Stockh)* 1983;95:117-22.

71. Ståhlberg MR. The influence of form of day-care on occurrence of acute respiratory tract infections among young children. *Acta Paediatr Scand [Suppl]* 1980;69(suppl 282).

72. Vinther B, Elbrønd O, Brahe Pedersen C. A population study of otitis media in childhood. *Acta Otolaryngol [Suppl]* (Stockh) 1979(suppl 360):135-7.

73. Ståhlberg M, Ruuskanen O, Virolainen E. Risk factors for recurrent otitis media. *Pediatr Infect Dis* 1986;5:30-2.

74. Watkins CJ, Leeder SR, Corkhill RT. The relationship between breast and bottle feeding and respiratory illness in the first year of life. *J Epidemiol Community Health* 1979;33:180-2.

75. Saarinen UM. Prolonged breast feeding as prophylaxis for recurrent otitis media. *Acta Paediatr Scand* 1982;71:567-71.

76. Coles EC, Cotter S, Valman HB. Increasing prevalence of breast-feeding. *Br Med J [Clin Res]* 1978;2:1122.

77. Toubbeh JI. Otitis media in the American Indian and Alaska native populations. In: Cole L, Deal V, eds. Communication disorders in multi-cultural populations. Rockville, Md: American Speech, Language, and Hearing Association, 1990 (in press).

78. Stewart JL. Otitis media in the first year of life in two Eskimo communities. *Ann Otol Rhinol Laryngol* 1989;98:200-1.

79. United States Congress. Office of Technology Assessment. Indian health care. Washington, DC: US Government Printing Office, 1986.

80. Doyle WJ. A functional-anatomic description of eustachian tube vector relations in four ethnic populations: an otologic study [Dissertation]. Pittsburgh, Pa: University of Pittsburgh, 1977.

81. Shaw JR, Todd NW, Goodwin MH, King GH. Observations on otitis media among four Indian populations in Arizona. In: Proceedings of the Second National Conference on Otitis Media. Columbus, Ohio: Ross Laboratories, 1979:91-102.

82. Otitis Media Project Reports, Department of Family and Community Medicine. Tucson, Ariz: University of Arizona Health Sciences Center, 1974-1982.

83. Todd NW, Feldman CM. Allergic airway disease and otitis media in children. *Int J Pediatr Otorhinolaryngol* 1985;10:27-35.

84. Goodwin MH, Shaw JR, Feldman CM. Distribution of otitis media among four Indian populations in Arizona. *Public Health Rep* 1980;95:589-94.

85. Shaw JR, Todd NW, Goodwin MH, Feldman CM. Observations on the relation of environmental and behavioral factors to the occurrence of otitis media among Indian children. *Public Health Rep* 1981;96:342-9.

86. Hayman C, Kester F. Eye, ear, nose and throat infections in natives of Alaska. *Northwest Med* 1957;56:423.

87. Department of Health and Welfare, Children's Bureau

DHECO. The McGrath project: A demonstration study on prevention of upper respiratory disease. State of Alaska Dept of Health and Children's Bureau. Washington, DC: US Government Printing Office, 1962.

88. Kimball BD. Ear pathology and hearing loss in an Alaska native high school. *Audionews* 1977;July:2.

89. Middaugh J, Ryan C, Metzler C, Dixon C. Otitis media and hearing impairment among selected racial groups in Alaska. Alaska Division of Public Health Report, April 1983.

90. Feasibility study. The prevention, recognition and treatment of otitis media among children of the Pacific Basin. Honolulu, Hawaii: University of Hawaii, 1983.

91. Wiet RJ, DeBlanc GB, Stewart J, Weider DJ. Natural history of otitis media in the American native. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):14-9.

92. Nelson SM, Berry RI. Ear disease and hearing loss among Navajo children — a mass survey. *Laryngoscope* 1984;94:316-23.

93. Thomson N. Aboriginal health — current status. *Aust N Z J Med* 1984;14:705-18.

94. Sunderman J, Hayden D. Chronic ear disease in Australian aborigines. *Med J Aust* 1984;140:708-11.

95. Hamilton MA, McKenzie-Pollock M, Heath M. Aural health in 227 Northland school and preschool children. *N Z Med J* 1980;91:59-62.

96. Eldridge R, Brody JA, Wetmore N. Hearing loss and otitis media on Guam. *Arch Otolaryngol* 1970;91:148-53.

97. Stewart J, Garret JA, Koegel PN. Hearing loss and otitis media on Guam: impact of professional services. Presented at the meeting of the American Speech-Language-Hearing Association, Washington, DC, November 1985.

98. Dever G, Stewart J, David A. Prevalence of otitis media in selected populations on Pohnpei: a preliminary study. *Int J Pediatr Otorhinolaryngol* 1985;10:143-52.

99. Stewart J. Hearing disorders among indigenous peoples of North America and the Pacific basin. In: Taylor O, ed. *Nature of communication disorders in culturally and linguistically diverse populations*. Philadelphia, Pa: College Hill Press, 1985:237-76.

100. University of Hawaii Schools of Medicine, Nursing and Public Health. An evaluation of health systems in the Pacific insular jurisdictions of the US. Honolulu, Hawaii, 1984.

101. Taylor R. Health in the Pacific islands. Report by the Pacific Islands Development Program, East-West Center, Honolulu, Hawaii, 1985.

102. Territorial Comprehensive Health Plan: 1980-1985. Trust Territory of the Pacific Islands. Honolulu, Hawaii: University of Hawaii, 1980.

103. Smith D. Otitis media in the highlands of Papua New Guinea [Editorial]. *Papua New Guinea Med J* 1981;24:214-6.

104. Teele DW, Klein JO, Rosner B. Greater Boston Otitis Media Study Group. Epidemiology of otitis media during the first seven years of life in children in Greater Boston: a prospective cohort study. *J Infect Dis* 1989;160:83-94.

105. Casselbrant ML, Brostoff LM, Cantekin EI, et al. Otitis media with effusion in preschool children. *Laryngoscope* 1985;95:428-36.

106. Casselbrant ML, Brostoff LM, Cantekin EI, Ashoff VM, Bluestone CD. Otitis media in children in the United States. In: Sadé J, ed. *Acute and secretory otitis media*. Proceedings of the International Conference on Acute and Secretory Otitis Media. Part 1. Amsterdam, the Netherlands: Kugler Publications, 1986:161-4.

107. Cantekin EI. Algorithm for diagnosis of otitis media with effusion. *Ann Otol Rhinol Laryngol* 1983;92(suppl 107):6.

108. Cantekin EI, Mandel EM, Bluestone CD, et al. Lack of

efficacy of a decongestant-antihistamine combination for otitis media with effusion ("secretory" otitis media) in children. *N Engl J Med* 1983;308:297-301.

109. Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ. Efficacy of amoxicillin with and without decongestant-antihistamine for otitis media with effusion in children. *N Engl J Med* 1987;316:432-7.

110. Howie VM, Ploussard JH, Sloyer J. The "otitis-prone" condition. *Am J Dis Child* 1975;129:676-8.

111. Marchant CD, Shurin PA, Turczyk VA, Wasikowski DE, Tutihasi MA, Kinney SE. Course and outcome of otitis media in early infancy: a prospective study. *J Pediatr* 1984;104:826-31.

112. Marchant CD, McMillan PM, Shurin PA, et al. Objective diagnosis of otitis media in early infancy by tympanometry and ipsilateral acoustic reflex thresholds. *J Pediatr* 1986;109:590-5.

113. Fria TJ, Cantekin EI, Eichler JA. Hearing acuity of children with otitis media with effusion. *Arch Otolaryngol* 1985;111:10-6.

114. Northern JL, Downs MP. Hearing in children. 3rd ed. Baltimore, Md: Williams and Wilkins, 1984.

115. Naremore RC. Influences of hearing impairment on early language development. *Ann Otol Rhinol Laryngol* 1979;88(suppl 60):54-63.

116. Menyuk P. Design factors in the assessment of language development in children with chronic otitis media. *Ann Otol Rhinol Laryngol* 1979;88(suppl 60):78-87.

117. Elliott LL, Katz DR. Development of a new children's test of speech discrimination. St Louis, Mo: Auditec, 1980.

118. Nozza RJ. Infant speech-sound discrimination testing: effects of stimulus intensity and procedural model on measures of performance. *J Acoust Soc Am* 1987;81:1928-39.

119. Dobie RA, Berlin CI. Influence of otitis media on hearing and development. *Ann Otol Rhinol Laryngol* 1979;88(suppl 60):48-53.

120. Tos M. Upon the relationship between secretory otitis in childhood and chronic otitis and its sequelae in adults. *J Laryngol Otol* 1981;95:1011-22.

121. Tos M, Stangerup S-E, Andreassen UK. Size of the mastoid air cells and otitis media. *Ann Otol Rhinol Laryngol* 1985;94:386-92.

122. Tos M. Frequency of secretory otitis and histology of normal middle ear mucosa. *Int J Pediatr Otorhinolaryngol* 1979;1:241-8.

123. Tos M, Bondig P, Poulsen G. Tympanosclerosis of the drum in secretory otitis after insertion of grommets. A prospective, comparative study. *J Laryngol Otol* 1983;97:489-96.

124. Kenna MA. Epidemiology and natural history of chronic suppurative otitis media. *Ann Otol Rhinol Laryngol* 1988;97(suppl 131):8.

125. Kafka MM. Mortality of mastoiditis and cerebral complications with review of 3,225 cases of mastoiditis with complications. *Laryngoscope* 1935;45:790-822.

126. Rosenwasser H, Adelman N. Otitic complications. *Arch Otolaryngol* 1957;65:225-34.

127. Gower D, McGuirt WF. Intracranial complications of acute and chronic infectious ear disease: a problem still with us. *Laryngoscope* 1983;93:1028-33.

128. Lund WS. A review of 50 cases of intracranial complications from otogenic infection between 1961 and 1977. *Clin Otolaryngol Allied Sci* 1978;3:495-501.

129. Courville CB. Intracranial complications of otitis media and mastoiditis in the antibiotic era. *Laryngoscope* 1955;65:31-46.

130. Sorensen H. Antibiotics in suppurative otitis media. *Oto-*

laryngol Clin North Am 1977;10:45-50.

131. Alford BR, Cohn AM. Complications of suppurative otitis media and mastoiditis. In: Paparella MM, Shumrick DA, eds. Otolaryngology. 2nd ed. Vol 2. Philadelphia, Pa: WB Saunders, 1980:1490-509.

132. May M, Chandler S, James R. Infection: malignant external otitis and other inflammatory disorders. In: May M, ed. Facial nerve. New York, NY: Thieme, 1986:441-54.

133. Harker LA. Cholesteatoma: an incidence study. In: McCabe BF, Sadé J, Abramson M, eds. Cholesteatoma: First International Conference. Birmingham, Ala: Aesculapius, 1977: 308-9.

134. Severeid LR. Development of cholesteatoma in children with cleft palate: a longitudinal study. In: McCabe BF, Sadé J, Abramson M, eds. Cholesteatoma: First International Conference. Birmingham, Ala: Aesculapius, 1977:287-9.

135. Fria TJ, Cantekin EI, Eichler JA, Mandel EM, Bluestone CD. The effect of otitis media with effusion ("secretory" otitis media) on hearing sensitivity in children. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:320-4.

136. Seid AB, Sellars SL. The management of otogenic lateral sinus disease at Groote Schuur Hospital. Laryngoscope 1973;83: 397-403.

137. Kaleida PH, Bluestone CD, Blatter MM, et al. Sultamycin "ampicillin-sublactam" in the treatment of acute otitis media in children. Pediatr Infect Dis J 1986;5:33-8.

138. Klein JO, Teele DW. Isolation of viruses and mycoplasmas from middle ear effusions: a review. Ann Otol Rhinol Laryngol 1976;85(suppl 25):140-4.

139. Klein BS, Dollete FR, Yolken RH. The role of respiratory syncytial virus and other viral pathogens in acute otitis media. J Pediatr 1982;101:16-20.

140. Sarkkinen HK, Meurman O, Salmi TT, Puhakka H, Virolainen E. Demonstration of viral antigens in middle ear secretions of children with acute otitis media. Acta Paediatr Scand 1983;72:137-8.

141. Sarkkinen H, Ruuskanen O, Meurman O, Puhakka H, Virolainen E, Eskola J. Identification of respiratory virus antigens in middle ear fluids of children with acute otitis media. J Infect Dis 1985;151:444-8.

142. Chonmaitree T, Howie VM, Truant AL. Presence of respiratory viruses in middle ear fluids and nasal wash specimens from children with acute otitis media. Pediatrics 1986;77:698-702.

143. San Joaquin VH, Rettig PJ, Marks MI. Lack of Chlamydia trachomatis (CT) in upper respiratory tract infections of children. Pediatr Res 1982;16:153A.

144. Shehab ZM, Roy CG, Minnich LL, Wright AL, Taussig LJ, GHMA pediatricians. Chlamydia associated lower respiratory tract infections in children over one year of age. Pediatr Res 1985;19:304A.

145. Schaefer C, Harrison R, Boyce WT, Lewis M. Illnesses in infants born to women with Chlamydia trachomatis infection. Am J Dis Child 1985;139:127-33.

146. Hammerschlag MR, Hammerschlag PE, Alexander ER. The role of Chlamydia trachomatis in middle ear effusions in children. Pediatrics 1980;66:615-7.

147. Chang MJ, Rodriguez WJ, Mohla C. Chlamydia trachomatis in otitis media in children. Pediatr Infect Dis 1982;1:95-7.

148. Muldoon RL, Jaecker DK, Kiefer HK. Legionnaires' disease in children. Pediatrics 1981;67:329-31.

149. Howard JE, Nelson JD, Clashen J, Jackson LH. Otitis media of infancy and early childhood: a double-blind study of four treatment regimens. Am J Dis Child 1976;130:965-70.

150. Nelson JD, Ginsburg CM, Clashen JC, Jackson LH. Treatment of acute otitis media of infancy with cefaclor. Am J Dis Child 1978;132:992-6.

151. Odio CM, Kusmiesz H, Shelton S, Nelson JD. Comparative treatment trial of Augmentin versus cefaclor for acute otitis media with effusion. Pediatrics 1985;75:819-26.

152. Hendrickse WA, Kusmiesz H, Shelton S, Nelson JD. Five vs. ten days of therapy for acute otitis media. Pediatr Infect Dis J 1988;7:14-23.

153. Shurin PA, Kim CH, Fulton D, Marchant CD. Susceptibility of beta-lactamase-producing strains of Branhamella catarrhalis to selected, orally administered antimicrobial agents. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Philadelphia, Pa: BC Decker, 1984:283-5.

154. Shurin PA, Marchant CD, Kim CH, et al. Emergence of beta-lactamase-producing strains of Branhamella catarrhalis as important agents of acute otitis media. Pediatr Infect Dis 1983;2: 34-8.

155. Kovatch AL, Wald ER, Michaels RH. Beta-lactamase-producing Branhamella catarrhalis causing otitis media in children. J Pediatr 1983;102:261-4.

156. Frolund-Thomsen V, Olsen J, Sorensen H, Thomsen J. Bacteriology and antibiotics in acute suppurative otitis media. J Otolaryngol 1976;5:289-97.

157. Welliver RC. Allergy and middle ear effusions: fact or fiction. In: Bernstein JM, Ogra PL, eds. Immunology of the ear. New York, NY: Raven Press, 1987:381-9.

158. Reisman ER, Bernstein J. Allergy and secretory otitis media. Pediatr Clin North Am 1975;22:251-7.

159. Boden I, Higgins MW, Matthews KP, Keller JB. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan. J Allergy Clin Immunol 1974;53:27-33.

160. Bernstein JM, Lee J, Conboy K, Ellis E, Li P. The role of IgE mediated hypersensitivity in recurrent otitis media with effusion. Am J Otol 1983;5:66-9.

161. Friedman RA, Doyle WJ, Casselbrant ML, Bluestone CD, Fireman P. Immunologic mediated eustachian tube obstruction: a double-blind crossover study. J Allergy Clin Immunol 1983;71:442-7.

162. Fireman P. Eustachian tube obstruction and allergy: a role in otitis media with effusion? J Allergy Clin Immunol 1985; 76:137-40.

163. Doyle WJ, Friedman R, Fireman P, Bluestone CD. Eustachian tube obstruction after provocative nasal antigen challenge. Arch Otolaryngol 1984;110:508-11.

164. Doyle WJ, Ingram A, Fireman P. Histamine-induced eustachian tube obstruction in monkeys. J Allergy Clin Immunol 1985;76:551-6.

165. Still GF. Common disorders and diseases of childhood. London, England: Oxford University Press, 1910:17-8.

166. Woodbury RM. The relation between breast and artificial feeding and infant mortality. Am J Hyg 1922;11:668-87.

167. Hoefer C, Hardy MC. Later development of breastfed and artificially fed infants: comparison of physical and mental growth. J Am Med Assoc 1929;92:615-9.

168. Grulee CG, Sanford HN, Herron PN. Breast and artificial feeding. Influence on morbidity and mortality of twenty thousand infants. J Am Med Assoc 1934;103:735-9.

169. Chandra RK. Prospective studies of the effect of breast feeding on incidence of infection and allergy. Acta Paediatr Scand 1979;68:691-4.

170. Pukander J, Luotonen J, Timonen M, Karma P. Risk factors affecting the occurrence of acute otitis media among 2-3-

year-old urban children. *Acta Otolaryngol* (Stockh) 1985;100:260-5.

171. Teele DW, Klein JO, Rosner B. The Greater Boston Collaborative Otitis Media Program. Beneficial effects of breast feeding on duration of middle ear effusion (MEE) after first episode of acute otitis media (AOM). *Pediatr Res* 1980;14:494.

172. Klein JO. Prevention of persistent middle ear effusion: immunoprophylaxis. *Pediatr Infect Dis* 1982;1(suppl):S99-S106.

173. Paradise JL, Elster BA. Evidence that breast milk protects against otitis media with effusion in infants with cleft palate. *Pediatr Res* 1984;18:283A.

174. Cunningham AS. Otitis and breast-feeding [Letter to the Editor]. *J Pediatr* 1984;105:854-5.

175. Cunningham AS. Morbidity in breast-fed and artificially fed infants. II. *J Pediatr* 1979;95:685-9.

176. Cunningham AS. Morbidity in breast-fed and artificially fed infants. *J Pediatr* 1977;90:726-9.

177. Fosarelli PD, DeAngelis C, Winkelstein J, Mellits ED. Infectious illnesses in the first two years of life. *Pediatr Infect Dis* 1985;4:153-9.

178. Schaefer O. Otitis media and bottle-feeding. An epidemiological study on infant feeding habits and incidence of recurrent and chronic middle-ear disease in Canadian Eskimos. *Can J Pub Health* 1971;62:478-89.

179. Timmermans FJ, Gerson S. Chronic granulomatous otitis media in bottle-fed Inuit children. *Can Med Assoc J* 1980;122:545-7.

180. Persico M, Podoshin L, Fradis M, Golan D, Wellisch G. Recurrent middle-ear infections in infants: the protective role of maternal breast feeding. *Ear Nose Throat J* 1983;62:297-304.

181. Forman MR, Graubard BI, Hoffman HJ, Beren R, Harley EE, Bennett P. The Pima infant feeding study: breast-feeding and respiratory infections during the first year of life. *Int J Epidemiol* 1984;13:447-53.

182. Holmes GE, Hassanein KM, Miller HC. Factors associated with infections among breast-fed babies and babies fed proprietary milks. *Pediatrics* 1983;72:300-6.

183. Sauls HS. Potential effect of demographic and other variables in studies comparing morbidity of breast-fed and bottle-fed infants. *Pediatrics* 1979;64:523-7.

184. Bauchner H, Leventhal JM, Shapiro ED. Studies of breast-feeding and infections: how good is the evidence? *JAMA* 1986;256:887-92.

185. Winikoff B. Issues in the design of breast-feeding research. *Stud Fam Plan* 1981;12:177-84.

186. Simopoulos AP, Grave GD. Factors associated with the choice and duration of feeding practice. *Pediatrics* 1984;74(suppl 4):603-14.

187. Kovar MG, Serdula MK, Marks JS, Fraser DW. Review of the epidemiologic evidence for an association between infant feeding and infant health. *Pediatrics* 1984;74(suppl 4):615-38.

188. Jason JM, Nieburg P, Marks JS. Mortality and infectious disease associated with infant-feeding practices in developing countries. *Pediatrics* 1984;74(suppl 4):702-27.

189. Promotion of breast feeding. Recommendations of the Council of the Society for Pediatric Research (SPR) and American Pediatric Society (APS), and of the American Academy of Pediatrics (AAP). *Pediatr Res* 1982;16:264-5.

190. Ogra PL, Greene HL. Human milk and breast-feeding: an update on the state of the art. *Pediatr Res* 1982;16:266-71.

191. Jelliffe DB, Jelliffe EF. "Breast is best": modern meanings. *N Engl J Med* 1977;297:912-5.

192. Beery QC, Doyle WJ, Cantekin EI, Bluestone CD, Wiet RJ. Eustachian tube function in an American Indian population.

Ann Otol Rhinol Laryngol 1980;89(suppl 68):28-33.

193. Spivey GH, Hirschhorn N. A migrant study of adopted Apache children. *Johns Hopkins Med J* 1977;140:43-6.

194. Osterholm MT, Klein JO, Aronson S, Pickering L, eds. Infectious diseases in child day care: management and prevention. *Rev Infect Dis* 1986;8:513-679.

195. Stool SE, Randall P. Unexpected ear disease in infants with cleft palate. *Cleft Palate J* 1967;4:99-103.

196. Paradise JL, Bluestone CD, Felder H. The universality of otitis media in 50 infants with cleft palate. *Pediatrics* 1969;44:35-42.

197. Koch HF, Neveling R, Hartung W. Studies concerning the problem of ear diseases in cleft palate children. *Cleft Palate J* 1970;7:187-93.

198. Soudijn ER, Huffstadt AJC. Routine micro ear examination in cleft palate babies. In: Abstracts of the Second International Congress on Cleft Palate. Copenhagen, Denmark, Aug 26-31, 1973:152.

199. Soudijn ER, Huffstadt AJC. Cleft palates and middle ear effusions in babies. *Cleft Palate J* 1975;12:229-33.

200. Møller P. Hearing, middle ear pressure and otopathology in a cleft palate population. *Acta Otolaryngol* (Stockh) 1981;92:521-8.

201. Chaudhuri PK, Bowen-Jones E. An otorhinological study of children with cleft palates. *J Laryngol Otol* 1978;92:29-40.

202. Freeland AP, Evans DM. Middle ear diseases in the cleft palate infant: its effect on speech and language development. *Br J Plast Surg* 1981;34:142-3.

203. Strupler W. Middle ear deafness in infants with cleft palate. *Int J Pediatr Otorhinolaryngol* 1980;1:279-83.

204. Wayoff M, Chobaut JC, Simon C, Jacquot M: Oreille moyenne et division palatine (à propos de 230 observations). *J Fr Otorhinolaryngol* 1980;29:661-70.

205. Ushiro K, Honjo I, Haji T, Isshiki N, Kohda Y. Middle ear diseases in cleft palate children. *Nippon Jibiinkoka Gakkai Kaiho* 1982;85:805-10.

206. Riberti C, Baldo D, Tirone L, Collini M. Hearing changes in patients with cleft lip and palate: clinico-statistical contribution. *Pediatr Med Chir* 1984;6:131-6.

207. Paradise JL, Bluestone CD. Early treatment of universal otitis media of infants with cleft palate. *Pediatrics* 1974;53:48-54.

208. Passy V. Middle-ear effusions in patients with velopalatal insufficiency. *Ear Nose Throat J* 1978;57:490-5.

209. Frable MA, Brandon GT, Theogaraj SD. Velar closure and ear tubings as a primary procedure in the repair of cleft palates. *Laryngoscope* 1985;95:1044-6.

210. Hubbard TW, Paradise JL, McWilliams BJ, Elster BA, Taylor FH. [Letter.] *N Engl J Med* 1985;313:1353-4.

211. Bluestone CD. Eustachian tube obstruction in the infant with cleft palate. *Ann Otol Rhinol Laryngol* 1971;80(suppl 2).

212. Paradise JL. Middle ear problems associated with cleft palate: an internationally oriented review. *Cleft Palate J* 1975;12:17-22.

213. Paradise JL. Otitis media in infants with cleft palate. In: Wiet RJ, Coulthard SW, eds. Proceedings of the Second National Conference on Otitis Media. Columbus, Ohio: Ross Laboratories, 1979:62-6.

214. Bess FH, Schwartz DM, Redfield NP. Audiometric, impedance, and otoscopic findings in children with cleft palates. *Arch Otolaryngol* 1976;102:465-9.

215. Webster JC, Eldis F. Ear disease in relation to age in the cleft palate child and adolescent. *Clin Otolaryngol* 1978;3:455-61.

216. Webster JC. Middle ear function in the cleft palate patient. *J Laryngol Otol* 1980;94:31-7.
217. Ahonan JE, McDermott JC. Extended high-frequency hearing loss in children with cleft palate. *Audiology* 1984;23:467-76.
218. Gopalakrishna A, Goleria KS, Raje A. Middle ear function in cleft palate. *Br J Plast Surg* 1984;37:558-65.
219. Bluestone CD, Beery QC, Paradise JL. Audiometry and tympanometry in relation to middle ear effusions in children. *Laryngoscope* 1973;83:594-604.
220. Fria TJ, Paradise JL, Sabo DL. Evidence of conductive hearing loss in infants with cleft palate. Presented at the Tenth Annual Meeting of the Society for Ear, Nose, and Throat Advances in Children, Toronto, Canada, Nov 21-22, 1982.
221. Paradise JL, McWilliams BJ. Simplified feeder for infants with cleft palate. *Pediatrics* 1974;53:566-8.
222. Møller P, Dalen H. Middle ear mucosa in cleft palate children: a scanning electron microscopic study. *Acta Otolaryngol [Suppl] (Stockh)* 1979(suppl 360):198-203.
223. Paradise JL, Smith CG, Bluestone CD. Tympanometric detection of middle ear effusion in infants and young children. *Pediatrics* 1976;58:198-210.
224. Brooks DN. An objective method of detecting fluid in the middle ear. *J Int Audiol* 1968;7:280-6.
225. Shurin PA, Pelton SI, Klein JO. Otitis media in the newborn infant. *Ann Otol Rhinol Laryngol* 1976;85(suppl 25):216-22.
226. Giebink GS, Le CT, Paparella MM. Epidemiology of otitis media with effusion in children. *Arch Otolaryngol* 1982;108:563-6.
227. Gates GA, Avery C, Cooper JC, Hearne EM, Holt GR. Predictive value of tympanometry in middle ear effusion. *Ann Otol Rhinol Laryngol* 1986;95:46-50.
228. Hubbard TW, Paradise JL, McWilliams BJ, Elster BA, Taylor FH. Consequences of unremitting middle-ear disease in early life: otologic, audiologic, and developmental findings in children with cleft palate. *N Engl J Med* 1985;312:1529-34.
229. Paradise JL. Otitis media during early life: how hazardous to development? A critical review of the evidence. *Pediatrics* 1981;68:869-73.
230. Bennett M. The older cleft palate patient (a clinical otologic-audiologic study). *Laryngoscope* 1972;82:1217-25.
231. Watson DJ, Rohrich RJ, Poole MD, Godfrey AM. The effect on the ear of late closure of the cleft hard palate. *Br J Plast Surg* 1986;39:190-2.
232. Paradise JL. Primary care of infants and children with cleft palate. In: Bluestone CD, Stool SE, eds. *Pediatric otolaryngology*. Philadelphia, Pa: WB Saunders, 1983:924-30.
233. Stewart JM, Ott JE, Lagace R. Submucous cleft palate. *Birth Defects* 1971;7:64-6.
234. Taylor GD. The bifid uvula. *Laryngoscope* 1972;82:771-8.
235. Saad EF. The bifid uvula in ear, nose and throat practice. *Laryngoscope* 1975;85:734-7.
236. Shprintzen RJ, Schwartz RH, Daniller A, Hoch L. Morphologic significance of bifid uvula. *Pediatrics* 1985;75:553-61.
237. Silva P, Chalmers D, Stewart I. Some audiological, psychological, educational and behavioral characteristics of children with bilateral otitis media with effusion: a longitudinal study. *J Learn Disabil* 1986;19:165-8.
238. Needleman HL. Effects of hearing loss from early recurrent otitis media on speech and language. In: Jaffee BF, ed. *Hearing loss in children*. Baltimore, Md: University Park Press, 1977.
239. Craig H, Stool S, Laird M. Project "Ears": otologic maintenance in a school for the deaf. *Am Ann Deaf* 1979;124:458-67.
240. Stool SE, Craig HB, Laird MA. Screening for middle ear disease in a school for the deaf. *Ann Otol Rhinol Laryngol* 1980;89(suppl 68):172-7.
241. Stool S, Black FO, Craig H, Laird M. Otologic care in a school for the deaf. *Otolaryngol Head Neck Surg* 1981;89:651-7.
242. Cohen MM. The child with multiple birth defects. New York, NY: Raven Press, 1982.
243. Harada T, Sando I. Temporal bone histopathologic findings in Down's syndrome. *Arch Otolaryngol* 1981;107:96-103.
244. White BL, Doyle WJ, Bluestone CD. Eustachian tube function in infants and children with Down's syndrome. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. *Recent advances in otitis media with effusion*. Philadelphia, Pa: BC Decker, 1984:62-6.
245. Schachern PA, Shea DA, Paparella MM. Mucopolysaccharidosis I-H (Hurler's syndrome) and human temporal bone histopathology. *Ann Otol Rhinol Laryngol* 1984;93:65-9.